CLINICAL PHARMACOLOGY and THERAPEUTICS

volume 2 *number* 5 **September-October 1961**

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earlier detection of peripheral vascular disease

key to improved therapeutic response

In practically all peripheral vascular disease cases where marked occlusion with severe ulceration or frank gangrene has not developed, patients can be assured that excellent treatment is available and many symptoms can be relieved.[1] Routine palpation of peripheral pulses[2] and performance of clinical tests for peripheral arterial disease[3] will help earlier diagnosis. Consequently treatment can be instituted sooner, improving likelihood of a favorable response to therapy.

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myo-  -vascular relaxant

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VASODĪLAN'S record of safety and effectiveness in the management of peripheral vascular disease has been established clinically.[4-6] Clarkson and Le Pere report: "With strictly a clinical office approach, isoxsuprine [VASODĪLAN] was used in the treatment of 100 patients with peripheral vascular disorders. Definite clinical improvement was obtained in 89 per cent of these patients."[5] They further state: "In particular, the symptoms of pain, cramping, numbness, and cold were consistently relieved."[5]

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Supplied – 10 mg. tablets, bottles of 100; 2 cc. ampuls (5 mg./cc.) for intramuscular use, boxes of 6.

For complete details on indications, dosage, administration and clinical background of VASODĪLAN, see the brochure of this product available on request from Mead Johnson Laboratories, Evansville 21, Indiana.

References: (1) Lieberman, J. S.: GP *21*:133-143 (March) 1960. (2) DeWeese, J. A.: New England J. Med. *262*:1214-1217 (June 16) 1960. (3) Winsor, T.: Peripheral Vascular Diseases: An Objective Approach, Springfield, Illinois, Charles C Thomas, 1959, pp. 457-458. (4) Kaindl, F.; Samuels, S. S.; Selman, D., and Shaftel, H.: Angiology *10*:185-192 (Aug.) 1959. (5) Clarkson, I. S., and Le Pere, D. M.: Angiology *11*:190-192 (June) 1960. (6) Samuels, S. S., and Shaftel, H. E.: J.A.M.A. *17*:142-145 (Sept. 12) 1959.

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CLINICAL PHARMACOLOGY and THERAPEUTICS

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"Cyclophosphamide [Cytoxan] has proved a valuable addition to chemotherapeutic drugs available for the treatment of malignant diseases of the haemopoietic and reticuloendothelial systems.... Particularly effective in Hodgkin's disease, lymphosarcoma, chronic lymphocytic leukaemia, and myelomatosis...."[1]

"Objective data suggest that this agent [Cytoxan] has advantages not possessed by standard alkylating agents now in clinical use."[2]

"With the use of cyclophosphamide [Cytoxan] there is a relative lack of thrombocytopenia and a diminution in gastrointestinal side-effects, so that it may offer therapeutic advantages over other alkylating agents."[3]

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(1) Matthias, J. Q.; Misiewicz, J. J., and Scott, R. B.: Brit. M. J. *2*:1837-1840 (Dec. 24) 1960.
(2) Coggins, P. R.; Ravdin, R. G., and Eisman, S. H.: Cancer *13*:1254-1260 (Nov.-Dec.) 1960.
(3) Papac, R.; Petrakis, N. L.; Amini, F., and Wood, D. A.: J.A.M.A. *172*:1387-1391 (March 26) 1960.

DOSAGE: *For neoplasms relatively susceptible to Cytoxan* —Patients with lymphomas and other neoplasms believed to be relatively susceptible to Cytoxan therapy are given an initial dose of 2-3 mg./Kg./day intravenously. White blood counts and platelet determinations should be made daily or twice weekly and the dosage adjusted accordingly. Intravenous infusions should be continued for at least 6 days unless otherwise indicated. A leukopenia of between 1500 and 5000 cells per cu. mm. (or lower) may be expected between the tenth and fourteenth day. In the presence of a leukopenia of less than 2000/cu. mm. Cytoxan should be discontinued until the white cell count returns to 2000 to 5000 (usually within a week). Dosage is subsequently adjusted as indicated by the patient's objective response and the leukocyte count. If the patient is subjectively improved, if the size of the tumor has decreased, or if the white cells are satisfactorily maintained between 2000 and 5000/cu. mm. oral dosage may be instituted equivalent to intravenous dosage.

Thrombocytopenia is rarely observed on this regimen. If platelet counts of less than 100,000/cu. mm. are observed, the patient should be watched carefully. If platelets continue to decrease, Cytoxan should be discontinued.

The patient who has had previous treatment with alkylating agents, or x-ray, or is debilitated may be more susceptible to bone marrow depression, and initial Cytoxan doses should be more conservative than the above. Such patients should have more frequent hematologic evaluation. Good medical practice demands access to a reliable hematologic laboratory when using Cytoxan.

For neoplasms relatively resistant to Cytoxan—Patients with carcinomas and other malignant neoplasms believed to be less susceptible to Cytoxan therapy are given a dose of 4 to 8 mg./Kg./day intravenously. Unless there are indications to the contrary, this dose is continued for 6 days, then stopped. Leukopenia usually ensues on the tenth to fourteenth day after the first dose of Cytoxan. Thrombocyte reduction is not common, and platelets may actually increase. The leukocyte count promptly returns toward normal levels in most cases, and as it begins to increase, sufficient Cytoxan is administered to maintain it near 2000 to 5000/cu. mm. This may be accomplished by two intravenous injections weekly, or by oral administration, or by a combination of both routes. An oral dosage of 50 to 200 mg. daily or an intravenous injection of 5 mg./Kg. twice weekly will usually suffice.

The platelet and leukocyte counts should be followed carefully, and the prior treatment history of patients carefully evaluated as delineated above.

Leukopenia as a guide to adequacy of dosage—The best objective measure for dosage seems to be the number of circulating white blood cells. This is used as an index of the activity of the hematopoietic system, especially the bone marrow. The mechanism by which Cytoxan causes a reduction in the level of white blood cells is not known, but cessation of dosage results in an increase in the level, indicating that the hematopoietic system had not been permanently affected. When large doses (8 mg./Kg./day for 6 days) are given initially, the white cell count falls rapidly. Following the cessation of the 6-day course, the white cells may continue to decline for as long as 8 days and then increase. The reduction of the white cell count during Cytoxan therapy and its subsequent increase when therapy is discontinued can be repeated in the same patient. Maximal reduction in leukocyte count indicates the maximal permissible Cytoxan level for therapeutic effect. Leukopenic patients must be watched carefully for evidence of infection.

Total white blood cell and thrombocyte counts should be obtained 2 or more times weekly in order to evaluate therapy and to adjust dosage.

SIDE EFFECTS: Although Cytoxan is related to nitrogen mustard, it has no vesicant effect on tissue. It does not traumatize the vein when injected intravenously, nor does it cause any localized tissue reaction following extravasation. It may be administered intravenously, intramuscularly, intraperitoneally, intrapleurally or directly into the tumor, when indicated. It is apparently active by each of these routes.

Nausea and vomiting are common and depend on dose and on individual susceptibility. However, many investigators accept the nausea and vomiting in favor of maintaining maximal therapy. The vomiting can be controlled with antiemetic agents.

Alopecia is a frequent side reaction to Cytoxan therapy. It has been observed in 28% of the patients studied in this country. The incidence is greater with larger doses. The loss of hair may first be noted about the 21st day of therapy and may proceed to alopecia totalis. This effect is reversed following discontinuance of Cytoxan; during reduced maintenance therapy, hair may reappear. It is essential to advise the patient in advance concerning this effect of the drug.

Dizziness of short duration and of minor degree has occasionally been reported.

Leukopenia is an expected effect and can be used as a guide to therapy. Thrombocytopenia may occur, especially after large doses. The leukocyte or platelet counts of an occasional patient may fall precipitously after even small doses of Cytoxan, as with all alkylating agents. The drug should be discontinued in such patients and reinstituted later at lower dosage after satisfactory hematologic recovery has occurred. Prior treatment with x-ray or with other chemotherapeutic agents frequently causes an earlier or exaggerated leukopenia or thrombocytopenia after Cytoxan medication. Only rarely has there been a report of erythrocyte or hemoglobin reduction.

ADMINISTRATION: Add 5 cc. sterile water (Water for Injection, U.S.P.) to 100 mg. of Cytoxan in the sterile vial (add 10 cc. to 200 mg. vial). Shake, allow to stand until clear, remove with sterile syringe and needle and inject.

The freshly prepared solution of Cytoxan may be administered intravenously, intramuscularly, intraperitoneally, intrapleurally, or directly into the tumor. The solution should be administered promptly after being made but is satisfactory for use for three hours after preparation.

If the patient is receiving a parenteral infusion, the Cytoxan solution may be injected into the rubber tubing if the solution is glucose or saline.

No thrombosis or thrombophlebitis has been reported from injections of Cytoxan. Extravasation of the drug into the subcutaneous tissues does not result in local reactions.

PRECAUTIONS: Cytoxan should not be given to any person with a severe leukopenia, thrombocytopenia, or bone marrow infiltrated with malignant cells. It may be given with suitable precautions to patients who have had recent x-ray treatment, recent treatment with a cytotoxic agent, a surgical procedure within 2-3 weeks, or debilitated patients.

AVAILABILITY: Cytoxan is available as follows:

Cytoxan for Injection, 100 mg., a sterile dry-filled vial containing 100 mg. cyclophosphamide and 45 mg. sodium chloride. Packaged, 12 vials per carton.

Cytoxan for Injection, 200 mg., a sterile dry-filled vial containing 200 mg. cyclophosphamide and 90 mg. sodium chloride. Packaged, 12 vials per carton.

Cytoxan Tablets for oral administration, 50 mg., white, round tablets, flecked with blue for easy identification. Packaged, 100 tablets per bottle.

For a copy of the Cytoxan brochure, or other additional information on Cytoxan, communicate directly with the Medical Department, Mead Johnson Laboratories, Evansville 21, Indiana.

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Erythropoietin—a significant discovery in clinical hematology

A wealth of evidence now confirms the fact that red blood cell production is controlled by the hormone erythropoietin.[1-3] Demonstrated in human plasma,[4] erythropoietin has been shown to produce reticulocytosis,[1,5-7] increase utilization of the Fe^{59} isotope, and increase erythrocyte precursors in marrow cultures.[3,8]

ERYTHROPOIETIN FOUND TO CONTROL RED CELL FORMATION

erythropoietin levels—new criteria in diagnosis of anemia—Increased erythropoietin blood levels can be demonstrated in severe anemia and following the start of accelerated formation.[9] Soon thereafter, the effect of the higher levels appears as an increased erythroid marrow activity.[10] Since the hemopoietic marrow is capable of producing more red cells than normally required, many anemias may be due to inadequate erythropoietin levels—a result of subnormal production or excessive excretion.

how does erythropoietin affect iron metabolism? Absorption and utilization of iron are dependent upon the rate of bone marrow erythropoiesis which, in turn, is dependent upon erythropoietin levels.[11,12] Thus, the demand for iron created by accelerated erythropoiesis is satisfied by both increased gastrointestinal absorption and mobilization of storage iron. Inadequate erythropoietin levels would seemingly account for the frequently disappointing results with the use of iron alone in many of the anemias.

can medication increase erythropoietin levels? Cobalt has been shown to be strikingly effective in increasing the production of erythropoietin.[13,14] Cobalt-enhanced erythropoietin accelerates red cell production and improves iron utilization with a subsequent increase in hemoglobin and erythrocytes. The new concepts of the cause, diagnosis, and management of anemia may now be applied clinically on the sound basis of extensive studies published on RONCOVITE®—MF,* the therapeutic cobalt-iron hematinic.

(1) Gordon, A. S.: Physiol. Rev. **39**:1, 1959. (2) Erslev, A. J.: J. Lab. & Clin. Med. **50**:543, 1957. (3) Rosse, W. F., and Gurney, C. W.: J. Lab. & Clin. Med. **53**:446, 1959. (4) Gurney, C. W.; Goldwasser, E., and Pan, C.: J. Lab. & Clin. Med. **50**:534, 1957. (5) Rambach, W. A.; Alt, H. F., and Cooper, J. A. D.: Blood **12**:1101, 1957. (6) Gordon, A. S., **et al.**: Proc. Soc. Exp. Biol. & Med. **92**:598, 1956. (7) Erslev, A. J.: Blood **10**:954, 1955. (8) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L. F.: Blood **13**:55, 1958. (9) Stohlman, F., Jr., and Brecher, G.: Proc. Soc. Exp. Biol. & Med. **100**:40, 1959. (10) Kraus, L. M., and Kraus, A. P.: Fed. Proc. **18**:1051, 1959. (11) Bothwell, T. H.; Pirzio-Biroli, G., and Finch, C. A.: J. Lab. & Clin. Med. **51**:24, 1958. (12) Beutler, E., and Buttenwieser, E.: J. Lab. & Clin. Med. **55**:274, 1960. (13) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L.: Science **125**:1085, 1957. (14) Murdock, H. R., Jr., and Klotz, L. J.: J. Am. Pharm. A. (Scient. Ed.) **48**:143, 1959.

*Cobalt chloride (cobalt as Co 3.7 mg.), 15 mg. ferrous sulfate exsiccated, 100 mg.

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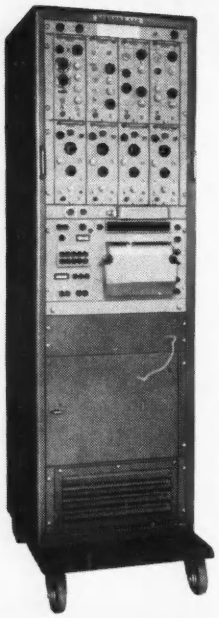

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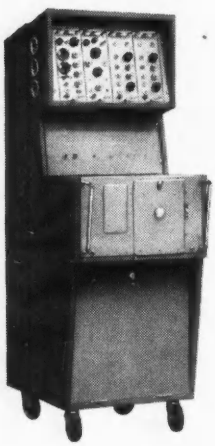

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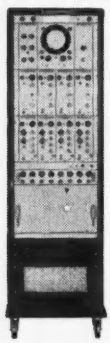

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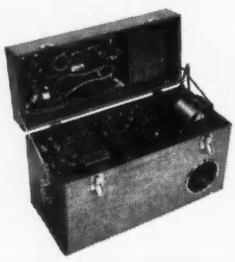

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CLINICAL PHARMACOLOGY and THERAPEUTICS

volume 2 *number* 5 **September-October 1961**

Editorial

A full cycle of diuretics

On the basis of what we know of the common clinical forms of edema and their treatment, in most instances the effect of a diuretic is primarily homeostatic rather than excretory. The ultimate purpose of therapy is not only to restore the size of the intercellular fluid compartment to its normal condition but more specifically to reduce the expanded stores of the fixed base, sodium, to normal. In accomplishing this, there are the homeostatic requirements that the anions excreted with the sodium be so proportioned that no specific anionic electrolyte or blood pH disturbance ensues and that the process be so highly particularized for the cation sodium that no other negative cation balance develops. However they accomplish it, effective diuretics induce a net sodium loss, the fluid loss being obligated by the process; the extent to which they approach the other requirements and the nature of other disturbances they induce vary widely.

There seems to be a compulsion to compose variations on the theme of effective diuretics already available which apparently derives from presumptions that there is need for greater natriuretic potency as well as for diuretics which cause less disturbance of other anion and cation relationships than those now in use. Beyond this, there is always the goal of developing a diuretic with no undesirable effects at all. This has resulted in the creation of a pride in new diuretics. It is interesting to examine how closely developments in diuretics during the past 40 or 50 years have approached these putative improvements.

To those suffering from edema, the simplest means of inducing diuresis—the elimination of sodium from the diet to a degree which leads to effective negative sodium balance, e.g., the Karell diet—also appears to be the least acceptable of all possibilities. Although this procedure is less likely than most others to lead to homeostatic difficulties, it lacks potency. But it works and, if pursued, is sometimes eminently satisfactory. The major difficulty with it is that it is untolerable to the modern jaded palate. A modification in the direction of satiating the demand for a salty taste while removing the salt from the food ingested through the use of cation exchange resins has been rejected after hopeful trial because of other gastrointestinal difficulties.

It thus appears at the very outset that in the therapeutic approach to a negative so-

dium balance to induce diuresis, the gastrointestinal tract may provide major stumbling blocks. It has, in fact, shaped much of the therapy of edema and has certainly stimulated a frenetic search for an orally acceptable diuretic.

Diuretics are no modern miracle, however. The real question about the new ones is: In what way are they superior to the old? Diuresis has been attributed to many ancient herbs, for there are a large number of natural diuretics. This was recognized by many long before the modern age of potent synthetic pharmaceuticals. Certainly the xanthines, the caffeine of coffee and tea, and the theobromine of cacao had been long recognized and universally used for their diuretic action and, as a matter of fact, still are. Where have these oldsters among diuretics failed, and where have the successors surpassed them?

The xanthines are in fact effective oral diuretics; all that is needed is a sufficiently large dose. They presumably increase the glomerular filtration rate as well as depress tubular resorption of sodium; an advantageous combination and a unique one too, for no other diuretic stimulates glomerular filtration, and this would appear to be a desirable as well as a logical point of attack in the treatment of cardiac edema, which is basically the consequence of a reduction of the glomerular filtration rate because of heart disease.

The xanthines induce diuresis through a saluretic effect, an increase in the excretion of sodium and chloride ions. In this, they resemble the mercurial diuretics. As the result of their intensive use, there may be a considerable loss of these ions, more especially of chloride, leading occasionally to hypochloremic alkalosis. While the development of this complication attests to their potency as diuretics, under ordinary circumstances it rarely happens, not only because these drugs are not commonly applied with sufficient intensity but also because their effectiveness is chloride dependent; when, because of their chloruretic action, blood chloride levels fall to critical levels, the xanthines become ineffective as diuretics, thereby preventing the further loss of chloride. This self-limiting effect of xanthines can be easily overcome by supplementation with ammonium chloride (or even sodium chloride), in that way replenishing the diminished chloride stores and restoring to the xanthine its diuretic vigor; at the same time, of course, the development of clinical hypochloremia is prevented. The xanthines are, therefore, effective diuretics with a built-in brake which tends to prevent the development of serious electrolyte imbalance. However, this self-limiting action does not become effective before a substantial diuresis has been induced. Clinically, this often means that moderately effective dosage of xanthine may be continued for an unlimited period of time, especially when supplemented with ammonium chloride.

What limits the effective clinical use of the xanthines as diuretics is the gastrointestinal distress which they all regularly induce at effective diuretic dosage. To a negligible degree only can this be overcome by the use of xanthines in suppositories. On the other hand, serious toxic effects have not been reported from their oral use, although intravenous administration has been associated with vascular reaction, especially after rapid injection. Central nervous system stimulation is rarely troublesome with theophylline or theobromine. To date, the xanthine structure has not been altered in such a way as to eliminate the gastrointestinal distress it causes. But it must be stated in all fairness that the same enthusiasm for modification of the structure of the xanthines has not been shown as with the more recent synthetic diuretics, especially the benzothiadiazines, more commonly called the thiazides.

When the diuretic activity of the mercurials was rediscovered by a Viennese nurse, a new era in diuretic therapy was opened up, not, as is generally assumed, merely because the mercurials were more potent than the xanthines but rather because the parenteral use of the mercurials

provided a method of circumventing the inevitable gastrointestinal distress of clinically effective doses of xanthines and thereby made it possible to treat edema more intensively than previously.

Although the organic mercurials do not stimulate glomerular filtration and induce saluresis through tubular depression alone, they are more potent depressors of tubular resorption than the xanthines. Consequently, their continued effective use tends to induce hypochloremic alkalosis. Although the mercurials are also chloride dependent and, in that sense, also have a self-limiting action, this does not develop until the blood chloride level is markedly depressed and after there has been an appreciable and prolonged diuresis. However, because of the acceptability of frequent effective parenteral doses of mercurial diuretics, electrolyte disturbances are more common with their intensive use than with the xanthines, especially when applied in conjunction with diets which markedly reduce sodium chloride intake. As with the xanthines, supplementation of mercurial diuresis with ammonium chloride tends to prevent clinical hypochloremia and its curbing effect on diuresis. Beyond this, the organic mercurials are not frequently associated with serious toxic effects. Despite their potency, fatal accidents have been rare, while the reported renal reactions have usually been questionable.

The major disadvantage of the organic mercurial diuretics is, by a strange turn, the same property which led to their use in preference to the xanthines, parenteral administration. While all mercurial diuretics are effective when given by mouth and by rectum, they provide by these routes even more serious gastrointestinal problems than the xanthines. However, in spite of all the newcomers, as a group they still are the most potent, most effective, most dependable diuretics. And in terms of effectiveness, they are eminently safe; certainly, in terms of their effectiveness, they are accountable for relatively few instances of electrolyte disturbance.

The introduction of an organic mercurial which could be administered subcutaneously rather than intramuscularly did not improve patient acceptability markedly. Structural variations on the theme of organic mercurials have not yet produced acceptable oral diuretics. As in the case of the xanthines, the search for such a one might have been pursued more intensively had not developments in entirely different pharmacologic areas seemed to have satisfied the demand for an effective and acceptable oral diuretic.

When introduced, acetazolamide, an entirely new diuretic entity, seemed to qualify as the first orally tolerable synthetic diuretic. It did not cause gastrointestinal distress. The basis of its pharmacologic action was novel: it was not saluretic; its major effect was to increase the loss of the bicarbonate ion together with the sodium and the water obligated by it. At the same time, there was chloride retention. As a result, the diuretic action of the drug tended to induce hyperchloremic acidosis. Since it enhanced potassium excretion, it tended also to induce hypopotassemia.

Although acetazolamide was used extensively and enthusiastically at first, its clinical use did not lead to difficulties in electrolyte balance along these lines, largely because of an extremely effective and promptly developing self-limiting action. Even with ceiling doses, the effectiveness of acetazolamide virtually disappears after 3 to 4 days. With the relative loss of bicarbonate and the accumulation of chloride ion, carbonic anhydrase inhibition becomes less effective, soon completely ineffective. As a result, not only is it not possible to maintain continued diuresis with it, but it is rarely possible to induce serious hyperchloremic acidosis or hypopotassemia with acetazolamide.

Here then is an acceptable oral diuretic which has limited usefulness because of internal braking mechanism which tends at the same time to prevent disastrous electrolyte disturbances and to prevent its own desirable action and not only does this

effectively but also very promptly, that is to say, the mechanism which tends to make it safe seriously curtails its effectiveness. Large numbers of structural variants on the acetazolamide theme have been examined, but the limitation described is clearly inherent in the nature of diuresis through carbonic anhydrase inhibition. And, therefore, while synthetic chemists have created a large number of effective carbonic anhydrase inhibitors, none of them have any advantage along these lines over acetazolamide.

Next came chlorothiazide. It is a unique drug, unique in that it combines in one drug two separate pharmacologic actions in such a way that each compensates for a limitation of the other. On the one hand, chlorothiazide exerts the carbonic anhydrase activity characteristic of acetazolamide, and on the other, it depresses a renal tubule transport system much in the same way as the xanthines and mercurials. Two different kinds of diuretic action inducing a net sodium loss develop from the same drug therefore, one inhibiting carbonic anhydrase and causing bicarbonate loss with chloride retention, the other causing chloride loss and sparing bicarbonate. As indicated in the cases of the xanthines and acetazolamide, each of these actions in itself is self-limiting as a diuretic process; yet, although carbonic anhydrase inhibition is the weaker of the two actions, in the combination, each complements the other in such a way that continued diuretic action is possible where alone each would soon cease because of its self-limiting action. Thus the chloride retention induced by carbonic anhydrase inhibition seems to prevent the tubule-depressant chloride-dependent action from subsiding, while the chloride loss and alkalotic tendency induced by tubule depression seem to maintain the drug's carbonic anhydrase inhibiting activity. Chlorothiazide, therefore, continues to induce diuresis so long as sodium excretion can be obligated by the removal of either the bicarbonate or the chloride ion.

The major undesirable effect of the diuresis induced by chlorothiazide is that caused by one of the drug actions chlorothiazide simulates which is not cancelled out by the other of the combination, namely, the potassium loss characteristic of carbonic anhydrase inhibition. And in this case, since the diuretic action of chlorothiazide is not self-limiting, continued use of the drug can and does induce hypopotassemia. Despite the relatively recent introduction of the drug, this has been a frequent clinical experience. Fortunately for chlorothiazide, hypopotassemia may be easily overcome by the concurrent oral administration of potassium chloride or even by the potassium in a large glass of orange juice at breakfast. Uncontrollable and unpredictable as a serious complication to the use of this drug is a problem which also applies to acetazolamide; both are related to the sulfonamide series, and, as is characteristic of the group, bone marrow depression and blood dyscrasias occasionally develop in hypersensitive patients. In addition, occurrence of hyperuricemia, with the precipitation of attacks of gout, has been reported.

Chlorothiazide does not cause gastric irritation. Its tendency to induce hypopotassemia can be easily overcome by the administration of potassium chloride. It is an effective oral diuretic which does not have a self-limiting action, so that it continues to be effective on maintenance dosage. It therefore also requires continuous attention if electrolyte disturbances are not to develop.

The major problems provided by chlorothiazide which seems to be bothering the pharmaceutical chemists are the matter of absolute potency and the tendency to induce hypopotassemia. Already, a large number of congeners of chlorothiazide have been synthesized, and nearly a score are already on the market; some are more than 100 times as potent as the parent material. Now as much diuresis can be induced with 10 or even 5 mg. of some of the newer members as with 1,000 mg. of chlorothia-

zide. But where the electrolyte composition of the urine produced in each case is the same, since the maximum diuresis obtainable from each is also identical, the dangers of electrolyte disturbance are also precisely the same, and the only advantage that one has over the other is the dubious one of requiring a smaller pill. This is the essential difference between chlorothiazide and hydrochlorothiazide.

The story does not end with the most potent chlorothiazide analogue, however. There is the search for one which does not cause kaliuresis and hypopotassemia. To provide this, there is a new series of congeners of chlorothiazide in which the ability to depress carbonic anhydrase activity is relatively or absolutely attenuated. In some of them, increased potency of the tubule-depressant facet of diuretic action makes the dose necessary to induce diuresis very small, so that the total carbonic anhydrase inhibition exerted by the small, absolute clinical dose is nil. As a result, potassium loss is also reduced to unimportance. So, too, is the complementary action of the two different sites of diuretic action. As carbonic anhydrase inhibition is reduced, their pharmacologic relationship with chlorothiazide becomes strained; these congeners hardly belong to the same pharmacologic group, one characterized by a combined action, any longer. Those analogues of chlorothiazide from which the carbonic anhydrase inhibitory activity has been effectively stripped now merely represent a diuretic that depresses tubular resorption much like a xanthine or a mercurial diuretic.

How indeed do they differ? Instead of the gastrointestinal distress of theobromine or an oral mercurial, they have as a potential the possibilities of inducing bone marrow depression, blood dyscrasias, and attacks of gout.

In the search for the perfect diuretic, one which is potent, dependable, and acceptable and which exerts *no other pharmacologic effect*, pharmacologists may be failing to make the most of the dependable and effective diuretics already available. One is constrained to wonder whether the taking of potassium chloride together with chlorothiazide and the need for carefully watching the patient justify all this pother about its congeners which somehow seems to be leading away from the breakthrough made by chlorothiazide. Is it not a good thing to have to watch a patient carefully and not to have a drug to give the patient so that he can be forgotten?

It seems clear that we may be completing the full circuit on the road to nowhere and have failed to follow through on new and significant discoveries in the field of diuretics. Instead we have steadily, though perhaps unconsciously, been making the new like the old. A new drug like chlorothiazide, which is both exciting as well as pharmacologically unique, has been "improved" upon until the "advantages" must be very loudly shouted because, like the Emperor's cloak, they are invisible largely because they are no longer there.

Walter Modell

Commentary

The newer penicillins

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The discovery of penicillin was like the opening of a new territory. Clinicians rushed in and began to mine the gold on the surface until no new ore was to be found. Then they moved on to fields where other antibiotics were being discovered. Meanwhile, chemists were exploring beneath the surface by changing the penicillin molecule. In the past 2 years, they have found gold in such depth to keep the clinicians busy for a long time. Thus we are poised at the start of a new gold rush, and we need a map of the penicillins to find the way. But the map that I shall spread is crude and incomplete because clinical explorations have been meager.

It took some time and a number of teams of research workers to find the structural formula of penicillin, but finally the one shown in Fig. 1 was agreed upon. The first changes were made in the salts, as shown on the right of Fig. 1. These were found to affect the solubility of the antibiotic. The soluble sodium and potassium salts are the ones most frequently used for intravenous therapy or direct instillation. The procaine salt delays absorption from an intramuscular site for a day or two, the benzathine salt for 2 to 4 weeks.

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But changes at the other end of the molecule have produced more important effects. In order to understand these, we must look at the structural formula again. Penicillin is a monocarboxylic acid with β-lactam and thiazolidine rings, attached through a CONH linkage to a prosthetic group, designated in Fig. 1 as *R*. The original penicillin, penicillin G or benzylpenicillin, has a benzene ring in place of *R;* another fermentation product penicillin V has a phenoxymethyl moiety. The portion of the molecule remaining after the removal of the prosthetic group is named 6-aminopenicillanic acid. This is an intermediary product in the process of fermentation that produces penicillin. The process can be stopped at this intermediate stage and the 6-aminopenicillanic acid isolated.[2] By the addition of various side chains, other penicillins can be prepared. These have been called synthetic; they are more accurately labeled semisynthetic. The best known among them are α-phenoxyethylpenicillin, officially named phenethicillin, and dimethoxyphenylpenicillin, officially named methicillin. Others have been made, and there are undoubtedly many to come.

How do these new penicillins differ from penicillin G? Because of certain structural weaknesses, the β-lactam ring of penicillin

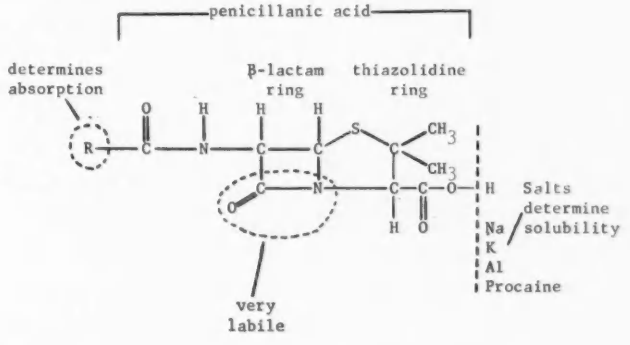
is easily broken, and when the ring opens, antibacterial activity is almost entirely lost. Penicillinase breaks this ring. Staphylococci that produce penicillinase are resistant to penicillin G because the penicillinase breaks the ring and inactivates the penicillin. Thus one can see the significant differences among the various penicillins by studying their action upon staphylococci.

When small inocula of penicillinase-producing staphylococci are incubated with penicillin G, the staphylococci grow well because the penicillin is rapidly inactivated by the penicillinase they produce. Under the same conditions, phenethicillin may check the growth of these staphylococci because small quantities of penicillinase inactivate phenethicillin at a slow rate only. But when a heavy inoculum is used, the large amounts of penicillinase formed will inactivate the phenethicillin and the staphylococci will grow profusely.[10]

Methicillin, on the other hand, is not inactivated by small and moderate amounts of penicillinase and only slightly by large amounts. Consequently, it is effective against staphylococci no matter how much penicillinase they produce. For example, Wallmark and Finland[33] showed that a penicillinase-producing strain of staphylococcus that inactivated penicillin G or phenethicillin in 10 minutes inactivated less than 10 per cent of methicillin after several hours of incubation.

Similar studies on other new penicillins have not been as complete, but present evidence seems to justify the classification of the penicillins into three groups, as shown in Table I. Benzylpenicillin (penicillin G) is the prototype for group I and phenethicillin for group II, while the only member of group III, for the present at least, is methicillin. It is interesting that the prosthetic group becomes progressively more complex as one moves from group I to group III. Thus, the prosthetic groups of the penicillins in group II apparently block some of the action of penicillinase upon the β-lactam ring, although not so completely as the more complex prosthetic group of methicillin.

The penicillins differ also in effectiveness against staphylococci that do not produce penicillinase and the other cocci that are affected by penicillin. Against these organisms, their effectiveness is in inverse ratio to their action on penicillinase-producing staphylococci. This was shown by Garrod[9] and by McCarthy, Wallmark, and Finland.[18] The latter investigators also reported that the amounts of phenylmercaptomethylpenicillin required to inhibit



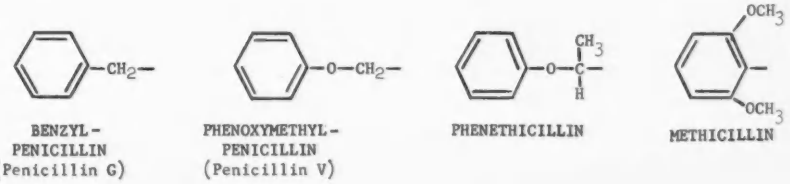
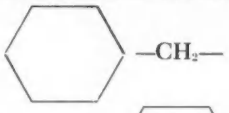
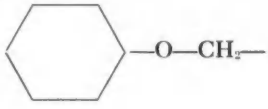
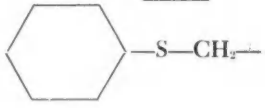
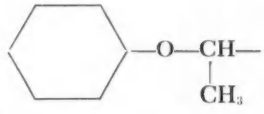
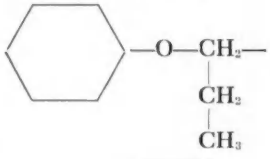
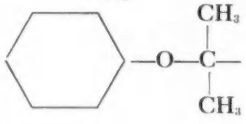
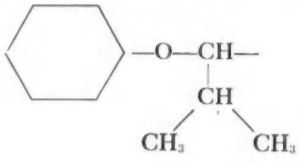
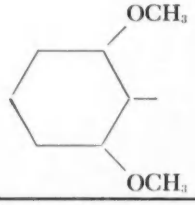


Fig. 1. Structure of the penicillin molecule and some of the important prosthetic groups.

Table I. *Effect of prosthetic groups of the penicillins upon their action on certain microorganisms*

Group	*Penicillin*	*Structural formula of prosthetic group*	*Inactivation by penicillinase*	*Action on staphylococci not producing penicillinase and on other cocci*
I	Benzylpenicillin (G)		Rapid and complete	Very effective
	Phenoxymethylpenicillin (V)			
	Phenylmercaptomethyl-penicillin			
II	Phenethicillin (α-phenoxyethylpenicillin)		Slow, but usually complete	Almost as effective as group I
	Phenoxypropylpenicillin			
	Phenoxyisopropylpenicillin[a]			
	α-Phenoxyisobutylpenicillin			
III	Methicillin (dimethoxy-phenylpenicillin)		Absent, or slow and incomplete	Moderately effective

[a] Phenoxyisopropylpenicillin has recently received the generic name potassium isopropicillin.

sensitive staphylococci, pneumococci, and group A streptococci were similar to the concentrations of penicillin G required. Williamson, Morrison, and Stevens[34] showed that the action of α-phenoxypropylpenicillin against these microorganisms was similar to that of phenethicillin.

How do these test tube phenomena compare with infections in patients? Again, it is best to separate the penicillins into groups. So far as penicillinase-producing staphylococci are concerned, penicillin V has not been any more effective than penicillin G. With respect to the penicillins in

group II, these are inactivated by penicillinase more slowly than penicillin G. Also, the concentrations of any of these penicillins attainable in the serum with customary doses will inhibit growth of some strains of penicillinase-producing staphylococci. Accordingly, it has been suggested that the penicillins in group II will be effective in some human infections caused by penicillinase-producing staphylococci. This is an extremely difficult hypothesis to test unless a large number of patients with these infections have been treated and the staphylococci studied carefully in each case. So far as I know, this has not been done with any of these penicillins. Therapy with α-phenoxypropylpenicillin (PA-248) has been reported in only a few patients, none of whom had bacteremia. While several reports[19, 30, 32] have appeared in which phenethicillin was successful in treating human infections, many of the infections were not caused by staphylococci, and many of the staphylococcal infections were so mild that the patients could have recovered without any antibiotic. Furthermore, tests were seldom done to see whether the staphylococci were penicillinase producers, in other words, whether penicillin G would have been successful. Until these proofs have been adduced, the clinician is well advised not to try to treat infections caused by penicillin-resistant staphylococci with the antibiotics in group II.

The recommendation has also been made that penicillin V or phenethicillin be used because it produces higher serum concentrations than penicillin G on oral administration. It is true that if similar doses of penicillins G and V are given, the concentration of penicillin V in the serum will be approximately twice as high as the concentration of penicillin G; also, concentrations of phenethicillin are generally higher than concentrations of penicillin V when the same doses are given.

But do these higher serum levels have any practical significance? The microorganisms against which penicillin is usually employed orally—group A streptococci, pneumococci, gonococci, and susceptible staphylococci— are affected by the usual therapeutic doses of any of these three penicillins. Thus, the concentrations of the antibiotics usually obtained in the blood are adequate, and higher concentrations produce no additional therapeutic effect. If penicillin G is given within ½ hour before or 1 hour after a meal, the concentrations in the serum may be too low to be effective. Therefore, patients receiving penicillin G should be instructed properly so that they do not take their doses near mealtime. If the physician is dealing with a patient who is not likely to follow such instructions, penicillin V or phenethicillin should be prescribed. Aside from this limitation, the choice between penicillin G, penicillin V, and phenethicillin in the treatment of infections caused by the susceptible microorganisms can be made on the basis of cost to the patient.

When high concentrations of penicillin are needed, either to ensure penetration into less accessible areas (as in meningitis or endocarditis) or because the microorganisms are relatively resistant to penicillin, parenteral penicillin will be selected as the reliable method of administration.

The possibility remains that there may be microorganisms of intermediate susceptibility which can be treated successfully with oral preparations that give higher serum concentrations than penicillin G. In bacterial endocarditis caused by alpha and gamma streptococci, penicillin V and phenethicillin have been advocated instead of intramuscular penicillin for use in conjunction with streptomycin. While this regimen has the advantage of decreasing the number of injections that a patient must receive, only a relatively few cases have been studied so far. Quinn and Colville's[21] series of 27 cases represents the largest group of patients with bacterial endocarditis treated with penicillin V. Twenty-five of these patients received streptomycin in addition, and 3 of the 25 were given intramuscular penicillin also. The patients were treated from 2 to 6

weeks. Clinical and bacteriologic cure occurred in 21 cases (77.8 per cent). These results are not as good as those reported by Hunter and Paterson,[11] who collected data on 146 patients with endocarditis caused by penicillin-sensitive streptococci who were treated for 2 weeks with a combination of intramuscular penicillin and streptomycin. Treatment failure or relapse occurred in only 6 per cent. Accordingly, while I would encourage further studies in this area, I would not recommend this as as optimal method of therapy in bacterial endocarditis until the results in a large number of patients are shown to be as good as those obtained with intramuscular penicillin and streptomycin.

For the treatment of penicillinase-producing staphylococci, methicillin seems to be the answer. Even here, the number of cases studied is not adequate for final judgment. Staphylococcal infections are not one disease but many, each having a different course and prognosis. The best test of an antistaphylococcal drug is in staphylococcal bacteremia. Twenty-five patients with staphylococcal bacteremia treated with methicillin have been reported in the literature,[4, 12, 15, 22, 25, 29, 31, 35] 12 of whom recovered. Five of the failures were in highly artificial situations in which Spitz-Holter valves,[4] which had been inserted to obtain a ventriculocaval shunt, became infected. My colleagues and I have observed six recoveries among 8 patients treated. If the patients with Spitz-Holter valves are excluded, the recovery rate among the remaining 28 patients is 64 per cent. This compares favorably with the recovery rate of 34 per cent in 112 patients with staphylococcal bacteremia treated with a variety of antibiotics during the past 10 years by Lepper and associates.[16]

Staphylococcal pneumonia is another testing ground for an antibiotic. Among 20 reported cases in adults,[6, 12, 22, 25, 29, 31] including 1 of our own, 16 patients recovered. This recovery rate of 80 per cent is only slightly better than that of 75 per cent observed in similar pneumonias treated by us with a variety of antibiotics in the past 10 years.*

Seven patients with proved or probable pneumococcal pneumonia are reported in the literature as having been treated successfully with methicillin. We have treated 11 patients with no failures. A variety of other infections have been treated successfully: streptococcal cellulitis and staphylococcal infections of the skin, osteomyelitis, bronchitis, emphysema, and meningitis, but, except for the last, none of these infections are universally fatal. Thus we cannot with certainty attribute the recoveries to methicillin until a larger number of patients have been treated. Nevertheless, methicillin at present appears to be the most promising antibiotic for staphylococcal infections since the discovery of penicillin G.

If methicillin is so effective, it will undoubtedly be used extensively. Will staphylococci appear that are resistant to the action of methicillin through some mechanism other than penicillinase? On the face of it, this seems to be a real danger. Barber[1] has pointed out that penicillin-sensitive staphylococci are twenty to fifty times as resistant to methicillin as to penicillin G. When other antibiotics that are in this range of efficacy have been used extensively, resistant forms of staphylococci have appeared. Such has been the case with the tetracyclines, chloramphenicol, erythromycin, and novobiocin. Might this not also happen with methicillin?

One way to test this is to try to train staphylococci to grow in high concentrations of methicillin. Some early reports minimized the possibility that staphylococci could be trained to grow in high concentrations of methicillin. Elek and Fleming[7] reported no increase in resistance after twenty passages. Knox[14] was able to grow a strain of *Staphylococcus aureus* in 18 μg of methicillin after three subcultures; but, at this point, the strain had lost its ability to form penicillinase and was sensi-

*H. F. Dowling, and M. H. Lepper: Unpublished data.

tive to penicillins G and V. Stewart[27] trained staphylococci to grow to the edge of a ditch containing methicillin in a concentration of 10 μg per milliliter but not to one containing 25 μg per milliliter. He later reported[28] that he had trained two of thirteen strains to grow in 10 μg per milliliter of methicillin after thirteen passages in solid media. After passage in liquid media, he was able to grow them in concentrations of 20 μg per milliliter but no higher.

On the other hand, Roberts, Allen, and Kirby[23] were able to increase the minimal inhibitory concentration of methicillin for two strains of staphylococci from 4 μg per milliliter to 32 and 64 μg per milliliter, respectively. Steinman,[26] by the use of special methods, increased the resistance to methicillin of a strain of *Staph. aureus* from 2 μg per milliliter to 350 μg per milliliter in six passages.

Fig. 2 shows the results obtained in our laboratory with a coagulase-positive strain of *Staph. aureus* and a coagulase-negative strain of *Staph. albus*. Both strains acquired the ability to grow in high concentrations of methicillin. The minimal inhibitory concentration of the coagulase-positive strain increased 256 times in fourteen passages, while the same increase in resistance was attained by the coagulase-negative strain in nine passages. It is of interest that the latter strain lost very little of its acquired resistance after fifteen passages in antibiotic-free medium.

We have been able to grow resistant forms of all of the strains of staphylococci that we have studied in vitro. In general, coagulase-negative staphylococci have become resistant more rapidly than coagulase-positive strains. Furthermore, while the colony size of some strains has diminished after they have been subcultured in increasing concentrations of methicillin, other strains have continued to grow luxuriantly after such subculturing. We must conclude, therefore, that staphylococci may acquire the property of circumventing the action of methicillin without a material

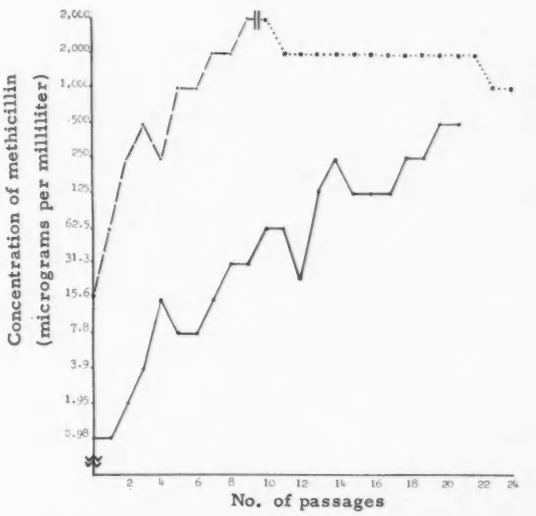


Fig. 2. Increase in resistance of a coagulase-negative and a coagulase-positive staphylococcus after passages in increasing concentrations of methicillin: (.—.) coagulase-positive staphylococcus, phage III (6/7/42E/53/42B,47C/77/M971); (.— —.) coagulase-negative staphylococcus, no phage type; (• · · •) coagulase-negative staphylococcus, passage in antibiotic-free medium.

change in their ability to grow. Infections in patients with such strains might not be amenable to methicillin therapy.

If we judge by what has happened when other antibiotics were used, the first evidence of increasing resistance among staphylococci is likely to appear in the hospital contacts of patients undergoing treatment. Elek and Fleming[7] sprayed 1 Gm. of methicillin into the air of a nursery four times a day. The percentage of infants with *Staph. aureus* in the nose declined from 50 per cent before the experiment to 2 per cent after 6 months. The noses of most of the patients became colonized with coagulase-negative staphylococci, and many of these were resistant to methicillin. No methicillin-resistant, coagulase-positive staphylococci appeared. None of the infants developed skin lesions caused by *Staph. aureus*, although fourteen such lesions appeared among control infants in wards where spraying was not done.

Since my associates and I[17] had observed the rapid rise of strains of *Staph. aureus* resistant to other antibiotics when these

antibiotics were used most extensively in a hospital ward, we decided to study the effects of methicillin in the same way. For the past 6 months, we have administered methicillin on our medical wards in all coccal infections. So far, we have cultured coagulase-negative staphylococci resistant to methicillin from the noses of only 7 nurses or patients not under treatment and coagulase-positive staphylococci from the noses of 2. The minimal inhibitory concentrations of methicillin for these strains varied from 15.6 to 250 μg per milliliter.

Jevons[13] found among 5,440 strains of staphylococci tested only three that were not inhibited by 10 μg disks of methicillin. The three strains were of phage type 7/47/53/54/75/77/ and were obtained from a nephrectomy wound, from the infected finger of a nurse, and from the nose of a patient in the same hospital. When tested by the tube dilution method, they required from 12.5 to 25 μg per milliliter of methicillin for inhibition. Only 1 patient in this hospital had been given methicillin at the time these strains were cultured.

Among 541 strains of *Staph. aureus* tested by several investigators in this country, seven required more than 6 μg per milliliter for inhibition of growth.[5, 8, 24, 25] None of these appeared after therapy with methicillin.

Although Roberts, Allen, and Kirby[23] were able to isolate strains from patients on the eleventh day of therapy in a case of osteomyelitis and also in a case of empyema, these strains were sensitive when tested in vitro.

Callaghan[4] studied 5 patients with bacteremia resulting from infected artificial valves for the drainage of cerebrospinal fluid into the superior vena cava. Although the bacteremia was not controlled by methicillin, the strains of *Staph. aureus* present in 2 cases showed no increase in resistance during therapy. The three strains of *Staph. albus*, however, showed a twofold to fivefold increase in resistance.

All staphylococci that we have cultured from the lesions or body fluids of patients after methicillin therapy have been sensitive to methicillin, except for *Staph. aureus* from the blood of a child with endocarditis who was admitted to the hospital after 12 weeks of methicillin therapy. This strain required 15.6 μg per milliliter of methicillin for inhibition of growth.

From the meager evidence available at present from the laboratory and the wards, we can conclude that coagulase-negative staphylococci resistant to methicillin are likely to appear where the antibiotic is used extensively. Since infections with these organisms are infrequent and seldom serious, this may not pose a great problem. On the other hand, the fact that they are sometimes introduced during surgical procedures and even venipunctures means that they have to be reckoned with. It is also apparent that strains of *Staph. aureus* that are resistant to therapeutic concentrations of methicillin do exist, although they are rare, and that continued use of methicillin may be followed by the spread of these strains within hospitals.

Because of this possibility, methicillin has been recommended especially for the treatment of staphylococcal infections. In the course of studying the antibiotic, others as well as ourselves have had occasion to treat patients with other coccal diseases. Although the minimal inhibitory concentrations for pneumococci and streptococci are considerably higher than those observed when penicillin G is used, patients with pneumococcal pneumonia, streptococcal sore throat, and bacterial endocarditis caused by green streptococci have responded well. Since the differential between the minimal inhibitory concentration and the concentration achieved in the serum is much lower in the case of methicillin than in the case of penicillin G, the possibility of the appearance of resistant strains must be considered. Thus, it seems wiser to continue to use penicillin G in these infections.

Penicillin G may also be recommended for minor staphylococcal infections that develop outside the hospital. For serious

staphylococcal infections and those developing within the hospital (and therefore likely to be caused by staphylococci resistant to penicillin G), methicillin may be started as soon as cultures are taken. If in vitro tests should show that the staphylococcus is susceptible to penicillin G, that antibiotic could be substituted for methicillin.

In conclusion, among the newer penicillins, methicillin has shown the greatest promise because it has consistently been effective in vitro against staphylococci that are resistant to penicillin G, because preliminary clinical studies in human infections have given good results, and because strains of staphylococci resistant to methicillin have been encountered only occasionally. Although methicillin is effective in infections caused by pneumococci, group A streptococci, and green streptococci, it is recommended that for the present it be used only in infections caused by staphylococci that are resistant to penicillin G.

The studies on methicillin were done in collaboration with Drs. Mark H. Lepper, George G. Jackson, Roger P. Kennedy, and John M. Leedom, with the technical assistance of Miss Margaret Mellody, Miss Mary Rubenis, and Mrs. Peggy Dunbar.

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Clinical trials based on patients' preferences

A new test of statistical significance

When patients' preferences are used to assess the value of alternative treatments in a comparative clinical trial, tied preferences are often obtained as a result of the poor discriminatory ability of the experimental subjects. It is maintained that the weight attached to a given preponderance of positive choices for one treatment should decrease as the number of tied preferences increases. However, tied preferences are neglected altogether in two recommended sequential statistical tests, while the correction for ties used in another statistical test, based on the coefficient of concordance, actually causes the significance levels to increase with the number of ties. A new test of statistical significance is described which can be used in clinical trials based on patients' preferences, if large numbers of ties are recorded. The presence of tied preferences lowers markedly the significance levels obtained in this test. The errors which may be caused by neglecting tied preferences are shown to be quantitatively important.

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The introduction of large numbers of new drugs each year makes it increasingly difficult to choose the most satisfactory preparation from a number of alternatives each of which has similar pharmacologic properties. In such situations, patients' preferences are important, since they may be based on subjective unpleasant effects. In other cases, patients' preferences may represent the only way to assess the therapeutic action of a preparation. Methods of studying patients' preferences objectively are therefore of importance. Rushbrooke and colleagues[9] carried out a therapeutic trial in which the action of two hypnotic drugs, as compared with a placebo, was assessed by having the patients rank the preparations in order of preference. Snell and Armitage[10] later pointed out that the statistical method used by Rushbrooke and colleagues required modification if large numbers of tied preferences were present; they used, instead, a sequential technique for a trial of cough mixtures which neglected tied preferences altogether. Tied preferences were also neglected in two recent trials of hypnotic drugs by a similar sequential method.[8, 12]

Failure of subjects to make a definite choice between two or more alternative drugs is likely to occur frequently in therapeutic trials, since it is often difficult for patients to compare the relative strengths of subjective sensations experienced at different times. In such a therapeutic trial, a clinician would tend to attach less weight

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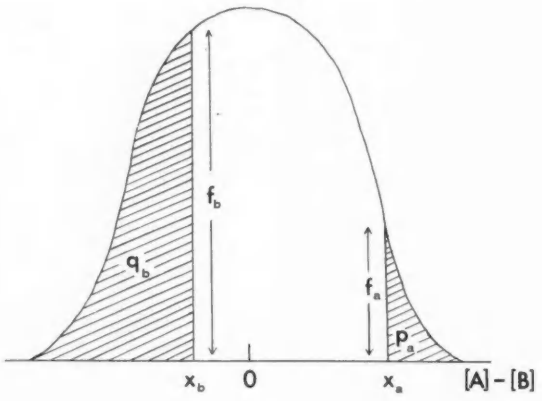

Fig. 1. Probability distribution for [A] – [B], the difference between the subjective effect of two drugs. If [A] – [B] $> x_a$, A is preferred to B; if [A] – [B] $< x_b$, B is preferred to A. If $x_b <$ [A] – [B] $< x_a$, a tied preference is recorded. The value p_a is the probability of observing a value greater than x_a for [A] – [B]; q_b is the probability of observing a value less than x_b for [A] – [B].

to a given preponderance of positive choices for one drug if large numbers of tied preferences were present, provided the group of patients being tested could be regarded as part of a homogeneous population.

This communication describes a statistical test in which tied preferences are taken into account in assessing statistical significance.

Statistical method

The method used by Rushbrooke and colleagues[9] consisted of two parts. The consistency with which different patients ranked the treatments in order of preference was first tested, using the coefficient of concordance, W. This test enabled the degree of agreement between the rankings accorded to each drug by each patient to be measured. A significant degree of agreement being present, a series of chi square tests was then performed to determine the contribution to this result of comparisons between relevant pairs of treatments.

A problem arises in the application of the W test when many tied rankings are present. In such cases, corrections are applied to the denominator of W and to the values assigned to the degrees of freedom, n_1 and n_2, in the subsequent z test.[6] The corrections cause the degree of agreement between subjects to increase with the number of ties, assuming that the number of definite choices remains the same, that is, the subjects are increasingly in agreement in being *unable* to distinguish between treatments. This type of agreement can be regarded as spurious in the context of a clinical trial where one is testing the significance of quantitative differences in the effect of different drugs, not the consistency of the judgments of a panel of judges.

Where only 2 subjects are carrying out a given ranking, there are available in Spearman's ρ test two types of correction for tied results corresponding to the two different situations defined above. However, there appears to be no simple way of expanding the argument from 2 to many subjects, except in the rather unlikely event that individual corrections for tied rankings are exactly the same in all observers.* It is clear that a different method of approach is required.

It is necessary to introduce the basic assumption that the differences between the subjective responses to two preparations, such as hypnotic drugs, can be measured only as rankings, since imperfect discrimination by the test subjects prevents the assessment of responses on some absolute scale. It is further assumed that there is a threshold value for the difference between the subjective responses to two preparations, [A] – [B], below which no distinction can be detected even though it may exist.

In statistical terms, it is postulated that each individual ranking represents a quantitative estimate of the difference between two subjective responses and that to describe the relevant population, such estimates are linearly related to the abscissa of a continuous probability distribution. If large numbers of ties are present, the situation can be represented graphically, as

*M. G. Kendall: Private communication, 1957.

in Fig. 1. The proportions of positive preferences for A and B are given by p_a and q_b, respectively. The criterion which determines whether there is a significant preponderance for one drug rather than another is then the difference from zero of the mean of the two quantiles, x_a and x_b, x_a being the upper quantile. Where [A] – [B], the difference between the subjective responses to the two drugs, is less than x_b, drug B is preferred to drug A. Where [A] – [B] is greater than x_a, A is preferred to B. Where [A] – [B] falls between x_a and x_b, a tie is recorded. The minimum detectable difference between two subjective responses is given by $\frac{1}{2}(x_a - x_b)$, the semi-interquantile range. There are, for large samples, the relations[7]

$$\text{Var } (x_a) = \frac{p_a\, q_a}{f^2_a\, n}$$

$$\text{Var } (x_b) = \frac{p_b\, q_b}{f^2_b\, n}$$

$$\text{Cov } (x_a, x_b) = \frac{p_a\, q_b}{f_a f_b n},$$

where x_a and x_b are, respectively, the upper and lower quantiles corresponding to the probabilities p_a and q_b (see Fig. 1); $q = 1 - p$; f_a and f_b are values for the ordinate of the probability distribution corresponding to x_a and x_b; n is the number of observations. Hence, for the standard error of the mean of the two quantiles in the case considered here, with n as the number of comparisons:

$$\epsilon' = \sqrt{\frac{1}{n}\left(\frac{p_a\, q_a}{f^2_a} + \frac{p_b\, q_b}{f^2_b} - 2\,\frac{p_a\, q_b}{f_a f_b}\right)}.$$

Values of the quantiles x_a and x_b, corresponding to p_a and q_b, are obtained from tables of the standardized normal distribution. One-tailed quantiles must be used (Table IX of Fisher and Yates[4]; the tabulated figures must be decreased by 5 to convert them from probits to standardized normal deviates). Values for f_a and f_b are then obtained from a table of ordinates of the normal distribution (Table II of Fisher and Yates[4]). The value of $\frac{1}{2}(x_a + x_b)$ is then compared with its standard error, ϵ', using normal distribution tables.

It would be expected that the minimum detectable difference between two sensations would vary randomly from patient to patient. It can reasonably be assumed that such variation would form a continuous distribution. In groups of patients, this variation would be described by changes in the value of $\frac{1}{2}(x_a - x_b)$, the standard error of which is half that of $\frac{1}{2}(x_a + x_b)$. It follows that variations in the average degree of discrimination in different groups of patients are reflected quantitatively by correspondingly different estimates of ϵ', the standard error of $\frac{1}{2}(x_a + x_b)$. It is in keeping with conventional procedure to use the standardized normal distribution throughout, since the frequency distributions underlying the quantitative reactions of subjects in preference trials cannot be accurately specified. This statistical approach bears an obvious relation to the methods used for "all or none" data in biologic assay which are based on the original work of Gaddum.[5]

It has been pointed out* that the statistical model described resembles that associated with the psychologic scaling procedure of Fechner, particularly as modified by Thurstone,[13] in which the probability of preferring one alternative to another is related to the difference between values of the alternatives on some numerical scale. However, the present model refers to a significance test in which the null hypothesis is made that there is no difference between two alternatives. Hence, the relation between the intensity of a stimulus and the subjective estimate of its magnitude (see Stevens[11]) does not enter into the question. It has, however, been shown that the sensitivity of observers may not be uniform over the whole range of a scale of subjective magnitude. Such scales are derived from the median (subjective) estimates of the magnitudes of different stimuli in groups of subjects and are assumed to have ab-

*By a referee.

Table I. *The effect of increasing numbers of tied preferences on the probability (P) of observing fixed numbers of positive preferences for two drugs, A and B*

Numbers of preferences			p_a	q_b	x_a	x_b	f_a	f_b	ϵ'	$\frac{x_a + x_b}{2\ \epsilon'}$	P
B	Tie	*A*									
13	0	27*	0.675	0.325	−0.454	−0.454	0.360	0.360	0.206	−2.205	0.0299
13	20	27	0.450	0.217	0.126	−0.784	0.396	0.294	0.177	−1.862	0.0656
13	60	27	0.270	0.870	0.613	−1.126	0.331	0.212	0.182	−1.408	0.1653
13	100	27	0.193	0.901	0.867	−1.323	0.274	0.166	0.176	−1.295	0.1964
13	610	27	0.042	0.980	1.733	−2.054	0.089	0.048	0.142	−1.132	0.2610

See Fig. 1 and the text for explanation of the symbols.

*Chi square value = 4.9; P = 0.0299. In this case, $x_a = x_b$, $f_a = f_b$, and $q_b = 1 - p_a$, since there is only one quantile.

solute validity independent of subjects. Since a stimulus of constant size is postulated in the model for the significance test, the subjective magnitude of the stimulus on a scale of this kind would also be constant and independent of subjects. It can therefore be assumed that the sensitivity of different observers is the same in any one experiment. The test would give comparable results in different experiments, since the use of the standardized normal distribution would compensate for differences between the sensitivity of the observers at different points on any scale of subjective drug effect.

It has also been pointed out* that some consideration of the work of Coombs[3] would be pertinent to this discussion. Coombs used a test situation in which subjects (2 male and 2 female psychology students, naive with respect to the experimental problem) were asked to rank sets of four gray disks in order from the most preferred as a representative gray to the least preferred. In the event, each individual's concept of a representative gray turned out to be an intermediate gray with light grays on one side and dark grays on the other. In a large series of observations in a controlled experimental situation, it was shown that there was less inconsistency of preference between pairs of gray disks when both members of a pair were on the same side of the individual's ideal gray than when they were on opposite sides of his ideal. These findings would seem to be in keeping with common sense expectation. However, it should be noted that Coombs' subjects were specifically asked to rank the gray disks in order from the most preferred *as a representative gray* to the least preferred. Thus the concept of an ideal gray was necessarily built into Coombs' model as a result of the instructions he gave the subjects. The analogous concept of an ideal drug effect would not appear to be built into the test situation when patients are asked simply to state which of a pair of drug preparations they prefer. Hence, it may reasonably be concluded that Coombs' results are not relevant to clinical trials conducted on such a basis and that the psychophysical model described previously is of general applicability in this type of investigation.

Where no ties are present, a significance test based on the standard error of a single quantile, $\epsilon' = \frac{1}{f}\sqrt{\frac{pq}{n}}$, gives the same significance level as the chi square test for a given series of observations. In Table I, an imaginary example is constructed in which the respective numbers of positive preferences for two alternative treatments remain the same, 27 and 13, respectively, while the number of tied preferences increases. The ϵ' test, described in the previous paragraph, is then applied. The probability of observing by chance as great or

*By a referee.

greater differences between the numbers of positive preferences for the two treatments is thus seen to increase from 0.03 to 0.26 as the number of ties increases from zero to 610.

Discussion

Snell and Armitage,[10] Thomson,[12] and Parsons and Thomson[8] used for their clinical trials sequential methods based on the usual significance test for the difference between proportions. Certain additional assumptions were made by Snell and Armitage in order to guarantee that the sequential trial would invariably reach a conclusion of some sort by the time a specified number of observations had been made.[1, 2] In all three investigations, the preferences of each subject were paired off, tied preferences being disregarded on the grounds that they do not contribute to the making of a final decision that one or another treatment should be adopted. This procedure represents a deliberate biasing of the observations in the direction toward which they may tend to run, in order to reach a quick decision. Results are thereby discarded that help in assessing the degree of error to which the observations are subject. For instance, each of the examples in Table I would be expected to give, on the average, the same result in a sequential plot using the method of Snell and Armitage, although they differ considerably in statistical significance as measured by the ϵ' test described previously. It is true that sequential tests are not strictly comparable with significance tests based on samples of fixed size. Nevertheless, it would seem reasonable not to discard tied preferences in a sequential test on purely theoretic grounds but to use them in laying down the operating characteristics for a test of this type.

For the purpose of the statistical test described in the previous section, it is assumed that the subjective difference between two sensations may have to reach a threshold value before it is recorded as a positive preference. Factors affecting the patients subjectively, other than those studied, may be expected to be randomly distributed and hence would cause, on the average, equal numbers of positive preferences for either alternative, where the threshold difference in the subjective sensation was exceeded. The ϵ' test described is very sensitive to the presence of tied preferences, as is shown by the examples given in Table I. Table II has been prepared from the data obtained by Snell and Armi-

Table II. *Trial of two cough mixtures*

Determination	*Trial*		
	Linctus pholcodine versus placebo	*Linctus diamorphine versus placebo*	*Linctus pholcodine versus linctus diamorphine*
Preference			
Pholcodine	22		17
Diamorphine		18	10
Placebo	6	4	
Tied	17	23	18
Chi square value	9.143	7.682	1.815
P (chi square)	0.004*	0.008*	0.184 N.S.
$\frac{\frac{1}{2}(x_a + x_b)}{\epsilon'}$	2.276	1.937	1.051
P (ϵ')	0.024†	0.054 N.S.	0.294 N.S.

Data of Snell and Armitage.[10] The tabulated figures are the numbers of patients recording each type of preference. The chi square values were calculated from the positive preferences only.

*Significant.

†Probably significant.

N.S. = not significant.

tage[10] in a therapeutic trial of two cough mixtures. In each comparison, approximately the same proportion of patients was unable to decide which of two alternatives was preferable. This finding is consistent with the above assumption.

The chi square values in Table II are calculated from the positive preferences only. The result of the comparison between linctus pholcodine and placebo shows a difference between preparations which is significant by the chi square test ($P < 0.01$) but only probably significant by the ϵ' test ($P < 0.05$), which takes tied preferences into account. The result of the comparison between linctus diamorphine and placebo shows a significant difference between preparations by the chi square test ($P < 0.01$), but this difference fails to achieve statistical significance in the ϵ' test ($P > 0.05$). The comparison between linctus diamorphine and linctus pholcodine does not give a statistically significant difference by either test. However, the value for P obtained by the chi square test is again lower than that obtained by the ϵ' test.

These findings demonstrate that the neglect of tied preferences in therapeutic trials based on patients' preferences may have a considerable effect on the conclusions drawn from them. The ϵ' test described in this communication makes use of tied preferences in testing for statistical significance. Furthermore, it allows for variation in the discriminatory ability of different groups of patients and enables this variation to be estimated quantitatively.

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An assessment of the responses to drugs acting on the central nervous system

A quantitative assessment of the subjective and objective responses to caffeine, secobarbital (quinalbarbitone), thiopropazate, and a placebo has been carried out in normal subjects. The order of administration of the drugs was randomized, but the actions of the drugs were explained to the subjects. The subjects were asked to describe the effects of the drugs and to assess which drug they had received on each occasion. It was found that there was an association between the actions of the drugs and the subjects' opinions about which drugs they thought they had received. When they guessed correctly, they responded to it vigorously; where they guessed incorrectly, the effects of the drug were partially or completely inhibited. The implications of this observation are discussed. The percentage of placebo reactors was within the normal range, and it is suggested that their symptoms may be related to the stress induced at the beginning of the experiment.

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Considerable difficulties are inherent in the assessment of the action of drugs on the central nervous system, since the effects which the drugs may be capable of producing are essentially of a subjective nature and it is difficult to design reliable and comprehensive measurements of their effects. This occurs particularly in the case of analgesic and hypnotic drugs, the actions of which can only be described by the subjects in whom they are being tested. In order to try to obtain quantitative values for the potency of different compounds, subjects are asked to compare the effects of new compounds with those of established drugs. Ranking methods as described by Wilson and his collaborators[16] for the trial of glutethimide and scoring methods as described by Houde, Wallenstein, and Rogers[9] for assessing the effect of analgesics have been used in order to make valid comparisons, but these investigators have pointed out how the results may be affected by the mental attitudes of the subjects and the environmental conditions associated with the tests. In both these tests, the subjects' descriptions of the effects of the drugs and their ability to discriminate between the potency of the different compounds formed integral components of the test methods. In order to provide some support for the subjects' state-

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ments about the actions of drugs, physiologic evaluations have been made while the subjects slept during testing of hypnotic agents[12] and measurements of physiologic changes have been carried out during testing of analgesic agents.[5] The results from both sets of experiments show that the subjective and physiologic evaluations gave different answers; in the tests on the pain threshold, indeed, such gross inconsistencies were obtained that statistical analysis was not justified. Each group of investigators placed greatest reliance on the subjective evaluation in their experiments.

The evaluation of hypnotic or analgesic agents is considerably easier than the evaluation of central nervous system stimulants and tranquilizers because with the former, the relatively all or none responses of sleep or relief of pain can be much more easily evaluated than feelings of stimulation or relaxation. The association of euphoria or dysphoria, and like or dislike, with the medication makes it difficult for the subjects to evaluate the drugs purely from the aspect of their classic pharmacologic action. This was emphasized by Lasagna, von Felsinger, and Beecher[14] for amphetamine. They stated that interpretation of the effect of this drug is greatly influenced by the experimental situation and mental attitude of the subjects, so that its action, as they observed it, differed considerably from that described in textbooks of pharmacology.

Definition of the action of tranquilizers in the human subject is even more difficult. There is little evidence about the effects of these drugs in normal people; normal people may however be involved in situations where stress, nervous tension, depression, and anxiety are engendered, for which a variety of tranquilizers and sedative drugs are recommended. Little is known about the meaning of these expressions and the factors which affect these states under normal conditions in human beings. It has however been pointed out by Modell and Houde[15] that the investigation of the pharmacologic actions of a drug in man is a necessary preliminary to its therapeutic evaluation. The evaluation of these drugs in patients with mental disease is confused by the paucity of information about the factors which influence mental states in normal people and the lack of knowledge about their effects on normal behavior patterns. As a result, the use of these drugs in the more complex situations presented in states of mental disease is considerably more difficult to evaluate than in normal people; similarly, the effects following administration, which are influenced by a combination of the disordered mental condition and the individual's reaction to his environment, are more difficult to interpret. The subjective descriptions on which the evaluation of the action of drugs depends is of the same nature in normal and mentally diseased individuals; because of lack of knowledge about the symptomatology in these two classes of individuals, drugs capable of producing mental effects are indiscriminately prescribed to both classes.

It is clear that the evaluation of all these classes of compounds is difficult because of the lack of definition of different mental states in man. Evaluation of subjective responses by clinical measurements is difficult because the relationship between the physiologic basis of mental states and the pharmacologic actions of drugs acting on the central nervous system is unknown. As

Table I. *Composition and description on the form of the compounds administered*

Compound	*Dose*	*Description of action given subject*
Lactose	Quantum sufficit	Inactive drug
Caffeine and lactose	300 mg.	Stimulating drug
Thiopropazate and lactose	20 mg.	Relaxant drug
Secobarbital sodium and lactose	120 mg.	Sleep-inducing drug

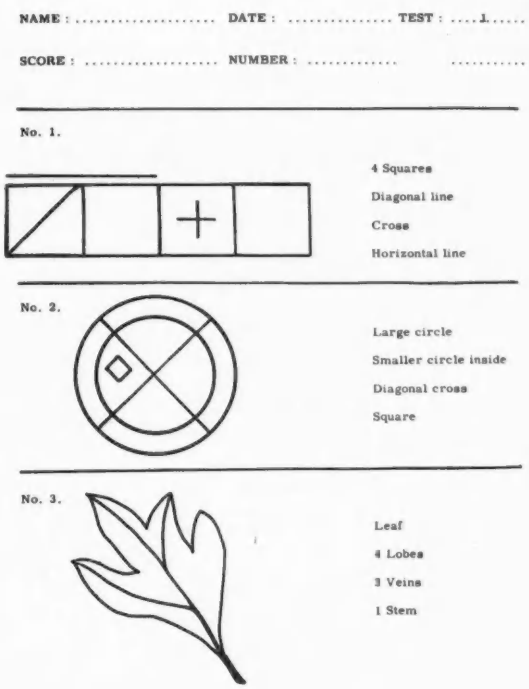

Fig. 1. The memory drawing test. Example of the drawings which it was necessary to memorize in 30 seconds and then reproduce in the test. In the scoring, four marks were awarded for each drawing; one mark was awarded for each of the characters described on the right when they were accurately reproduced in relation to the other characters of the drawings.

Beecher[1] has pointed out, there is a fundamental characteristic in the interaction between drug and patient. Until this characteristic has been investigated much more extensively, the actions of drugs on the central nervous system of man will lack definition. The important function of the placebo in clinical trials has been repeatedly emphasized, and the existence of subjects who react to the administration of a placebo has been recognized.[17] This reflects the important relationship between the mental make-up of man and his physiologic mechanisms. It is becoming clear that the clinical pharmacologist and clinician must now recognize that the experimental subject and patient can modify the action of drugs and that this psychologic mechanism may be as important in the assessment of drug action as the biochemical mechanisms by which man can modify the actions of drugs, to which Brodie has drawn attention.[3, 4]

In the present experiments, the effects of caffeine, secobarbital (quinalbarbitone), a tranquilizer (thiopropazate), and a placebo (lactose) have been examined in normal young adult subjects by use of a modification of the double blind technique. The effects of the drugs on the subjects were recorded, and the relationship between their pharmacologic actions and the subjects' impressions about which drugs they received were analyzed in order to define to what extent these impressions were capable of modifying the pharmacologic actions of the drugs.

Methods

The subjects were 54 volunteers, 25 men and 29 women, of whom the majority were university students. The remainder were members of the academic and technical staff of the university. They were told that they would do the experiment during four afternoon sessions at each of which they would receive a drug and that the drugs would be given to them in an order known neither to themselves nor to those who were conducting the experiment. They were also told that the compounds they would receive would be made up in the form of capsules and would comprise an inactive agent, a sleep-producing drug, a relaxant drug, and a stimulating drug. They were told that the sleep-inducing drug would make them feel sleepy, the relaxant drug would reduce feelings of worry and mental tension, and that the stimulating drug would make them feel more wakeful and enable them to think more quickly. They were told that no unpleasant or toxic effects were to be expected and that they would receive 25 shillings each when they had taken all the drugs and finished the tests. The compounds which were administered, their doses, and the corresponding written descriptions of their actions are shown in Table I. Caffeine and secobarbital were administered in doses within the range recommended in *The British Phar-*

Table II

Name _____ Date _____ Test _____

Number _____ _____ _____

Administration of drug: Date _____ Time _____

Please answer all the questions by writing yes or no in the spaces provided.

Answer before going to bed:

1. During the evening did you feel that
   You could work better than usual:
   You could work as usual:
   It did not matter whether you worked or not:
   You were too tired to do any work:
2. Do you feel
   Alert: Relaxed: Normal: Drowsy:
   Depressed: Hilarious: Anxious:
3. Do you feel
   Dizzy: That you have a headache:
   Stiff: Vision is blurred:

Answer the following morning:

4. Did you sleep better than usual:
   Did you sleep as usual:
   Did you remain awake more than usual:
5. Which drug do you think you received?
   The sleeping drug: The inactive drug:
   The relaxing drug: The stimulating drug:
6. Would you like to receive this drug again?
7. Describe shortly what you did and how you felt during the evening:

macopoeia. The dose of thiopropazate was twice the therapeutic dose recommended by the manufacturers for a single administration.

Three psychologic tests were done by each subject immediately before the first drug was taken and also 2 hours after each drug was administered. The initial tests were done in order to familiarize the subjects with the experimental procedure and also to give control results which would be unaffected by administration of any drugs. The psychologic tests comprised a test on extrasensory perception the details of which are described elsewhere by Huby and Wilson,[10] an arithmetic test, a memory drawing test, and a nonsense syllable memory test. In the arithmetic test, each subject was asked to do as many simple addition sums as possible during a period of 1 minute. One point was given for each correct answer; the possible total score was 20. In the memory drawing test, the subject was required to memorize a sheet of three drawings of which two were abstract and one was of a recognizable common object. After 20 seconds, the sheet was removed and it was required to reproduce the drawings from memory as accurately as possible. The maximum possible score for this test was 12; the scoring was necessarily rather arbitrary, but the drawings were constructed

to reduce this arbitrariness to the minimum (Fig. 1). In the nonsense syllable test, the subject was asked to memorize a list of ten nonsense syllables in 30 seconds. He was then given a list of forty syllables, which included the ten he had memorized, and was asked to mark the ten which he had just seen. He was given as long as he wished to do this. The syllables were chosen from published lists of three letter syllables which had been found to have very low associative values.[8, 11] This test was scored on a maximum of 10 points.

After each subject had done the psychologic tests, he was given a form which he was asked to complete the same evening before going to bed and the following morning when he got up. The form is reproduced in Table II. The subjects were required to return the completed form when they came to the next drug-taking session.

The double blind technique was used for the performance of the experiment, and the pharmacologic action of the drugs was described to the subjects. Lasagna[12] took the same precaution when comparing the action of hypnotic agents so that the amount and nature of suggestion might be reasonably uniform for all his subjects. The order of administration of the test drugs and placebo was randomized, and all the compounds were administered to all the subjects. Five sets of experimental test material were prepared; the subjects received a different set in each experimental session, the order of presentation having previously been determined from random number tables. All the compounds which were administered were made up in identical capsules and were identified by an alphabetic symbol. The key to their identification was withheld until all the tests had been finished and the forms corrected.

Results

To facilitate evaluation of the effects of the drugs on the experimental subjects, the results obtained from the investigations will be discussed in four sections: (1) the effects which the subjects reported on the form which they completed after taking the drug, (2) the subjects' opinions about which drug they received in each test (the relationship between what the subject thought he had received and what he had actually received will be discussed), (3) the results of the psychologic tests, and (4) the placebo reactions.

The effects of the drugs. The effects which the subjects observed and reported

Table III. *The effects of the drugs as reported affirmatively by the subjects on the forms*

Section	Effect	Drug			
		Lactose	*Caffeine*	*Thiopropazate*	*Secobarbital*
1	Could work better	3	9	4	3
	Could work as usual	34	33	22	21
	Work did not matter	17	15	15	17
	Too tired to work	4	4	21	20
2	Felt				
	Alert	12	20	7	14
	Relaxed	14	14	19	24
	Normal	42	34	27	17
	Depressed	8	4	6	3
	Drowsy	7	8	24	33
	Hilarious	2	7	1	5
	Anxious	1	5	3	1
3	Felt				
	Dizzy	1	6	2	23
	Stiff	2	2	4	0
	Had				
	Headache	10	8	6	7
	Blurred vision	4	4	4	11
4	Slept				
	Better	7	11	22	28
	As usual	37	28	31	22
	Remained awake	11	18	1	2
6	Would like to receive again	14	21	11	13
	Would not like to receive again	17	24	32	28
	Indifferent or did not reply	23	9	11	13

in their forms are summarized in Table III. The numbers of subjects who answered yes are shown in this table. Many of the subjects answered in the affirmative more than once in each section of the form; as a result the positive answers to some of the questions exceeded the total number of subjects taking part in the experiment.

These experiments were performed after the subjects had finished their final examinations. Many answered section 1 literally; they did not specify whether they felt that it did not matter whether they worked or not but answered whether actually it did matter or not. As a result, the answers to this part of the question were not considered to be accurate and, therefore, probably have little significance. The majority of the subjects stated that they experienced several symptoms in section 2. It was understood that these were descriptions of their physical state, and they were not regarded as alternatives. The number of subjects who complained of feeling stiff or having a headache was small but was highest amongst those who received lactose. It can therefore be concluded that these symptoms were not effects peculiar to any of the pharmacologically active compounds; some of the subjects indeed attributed their stiffness to playing tennis and other sports. The subjects' assessment of how well they slept after the different drugs varied considerably and, like the last question, in which the subjects were asked whether they would like to receive the drugs again, indicated that the drugs were having pharmacologic effects which the subjects could appreciate and did not always like.

Thiopropazate and secobarbital produced effects which differed from each other very little, and the majority of the subjects stated that they would not like to receive either of these drugs again. Caffeine tended to cause wakefulness, although this was often preceded by a feeling of drowsiness which lasted for an hour or two. Fewer subjects stated that they would not like to receive it again than was the case with thiopropazate or secobarbital, and in fact many of them specifically stated that they would like to receive this particular drug again. The over-all response to lactose showed that the subjects did not notice any extraordinary effects after receiving it.

The opinion of the subjects about the drugs they received. The following method for scoring the replies in the forms was used. Where the number of affirmative replies differed considerably in the case of two of the active drugs from the number for lactose, a value was given for that reply weighted according to its difference; a score proportionate to the difference was given for this reply to each of the drugs. If only one drug showed a difference, a score equivalent to twice this difference was given. The answers "would not like to receive again," and "indifferent" were not scored. Most of the replies for thiopropazate resembled those for secobarbital, but dizziness and blurred vision were characteristic of secobarbital, which therefore was weighted accordingly. Lactose was used as the reference drug in this method of scoring, so no scores for the effects resulting from this compound can be shown in the results.

The subjects were divided into groups to show which drug they had actually taken and which drug they thought they had taken. For each drug actually administered, the average score for the effects which could be attributed to each of the drugs which might have been received was obtained from the subjects' answers on the forms. Table IV shows the number of subjects who scored above average in each group. Henceforward, when reference is being made to the scores obtained from the subjects' answers on the forms which described the effects of the drug, the drug which was responsible for the score will be indicated in italic.

There are considerable differences in the numbers who scored above average, according to whether they thought they had received the drug which had been adminis-

Table IV. *Analysis of the effects of the different drugs*

Drug administered	*Drug thought taken*	*No. of subjects*	*No. scoring above average for the effects from the drugs below*					
			Caffeine		*Thiopropazate*		*Secobarbital*	
			No.	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*
Lactose	Inactive	29	4	14	1	3	1	3
	Stimulating	10	3	30	0	0	0	0
	Relaxant	10	2	20	2	20	2	20
	Sleep-inducing	4	2	50	4	100	4	100
Caffeine	Inactive	20	5	25	3	15	1	5
	Stimulating	17	15	89	0	0	1	6
	Relaxant	10	4	40	3	30	3	30
	Sleep-inducing	7	1	14	5	71	5	71
Thiopropazate	Inactive	15	0	0	2	13	2	13
	Stimulating	9	6	67	2	22	1	11
	Relaxant	11	0	0	7	64	5	45
	Sleep-inducing	19	1	5	16	84	16	84
Secobarbital	Inactive	6	1	17	2	33	2	33
	Stimulating	7	5	71	1	14	4	57
	Relaxant	15	6	40	9	60	13	87
	Sleep-inducing	25	1	4	22	88	20	80

Subjects are grouped according to the drug they received and the drug which they thought they had received. The number shown in column 3 indicates the number of subjects who thought they had received the drug shown in column 2 when they had in fact received the drug shown in column 1. Under the names of the drugs, in columns 4, 6, and 8, are shown the numbers of subjects who scored above the average score for the whole group in the answers on the forms.

tered or not. An attempt has been made to analyze the significance of this observation in Table V. The chi square test has been used to compare the numbers having scores above and below the average score of all the subjects for each drug, using the subject grouping employed in Table IV. In order to obtain sufficiently large numbers, it was necessary to combine some of the numbers to form cells for the construction of two by two tables for the chi square test. From the answers on the forms, it was concluded that there was considerable difficulty in distinguishing between the effects of secobarbital and thiopropazate. In the calculations, therefore, the numbers for those who thought they had received the sleep-inducing drug and those who thought they had received the relaxant drug have been combined. In the cases where thiopropazate and secobarbital were the drugs which were administered, this combined total for the sedative drugs has been compared with the combined total for those who thought they had received the stimulating and the inactive drugs. In the case where caffeine was the administered drug, it was clearly inappropriate to combine the numbers for the stimulating and the inactive drugs; in this case the combined total for the sedative drugs was compared with the number of subjects who thought they had received the stimulating drug. In some cases, the numbers were still too small for the chi square test to be applied; in these cases, if the difference in the numbers appeared to be striking, a comment to this effect has been made in the table.

From the results in Table IV, it is clear that there is an association between the pharmacologic actions of the drugs on the subjects and the subjects' impressions about which drug they had received. For example, when it was believed that the stimulating drug had been received the caffeine

had actually been administered, a large number of subjects scored above average for the effects from *caffeine* and very few scored above average for the effects from *thiopropazate* or *secobarbital*. When it was believed that thiopropazate or secobarbital had been received when one of the sedative drugs had actually been administered, larger numbers of subjects scored above average for the effects from these drugs than for the effects attributable to *caffeine*. On the other hand, when caffeine had been administered but it was believed that the sleep-inducing drug had been received, larger percentages of subjects reported effects attributable to *thiopropazate* and *secobarbital* than to *caffeine;* also, when the subjects thought they had received the stimulating drug after they had actually received secobarbital, the largest percentage of subjects scored above average for effects which could be attributed to *caffeine*. Statistical analysis of these results, insofar as it is possible with the numbers involved, indicates that they are highly significant (Table V).

It can therefore be concluded that the pharmacologic action of an administered stimulant or sedative drug generally occurred only when the subjects thought that they were in fact receiving this drug. If they thought they were receiving the sleep-producing drug when they had actually taken caffeine, the effects attributable to caffeine occurred less frequently; in other words, the action of caffeine tended to be inhibited. Similarly, the effects of the sedative drugs tended to be inhibited when the subjects thought they had received the stimulating drug.

The psychologic tests. None of the pharmacologically active drugs caused any significant change from the values for lactose, although secobarbital did cause a slight reduction in the scores in all three tests in comparison with lactose. Thiopropazate did not have any effect on the scores. The performance of the subjects improved steadily with practice in the arithmetic and memory drawing tests but deteriorated after the control session in the nonsense syllable memory test. This deterioration may be attributed to the fact that as the subjects were presented with more and more nonsense syllables, the increasing vocabulary made the process of selection of particular syllables more difficult. This may have compensated for the improvement resulting from practice which was observed in the other tests.

The placebo reactors. Forty-six per cent of the subjects thought they had received a pharmacologically active drug when they had in fact received lactose. The effects which they reported are shown in Table IV. When the subjects thought that they had received an active drug but had actually received lactose, they frequently re-

Table V. *Analysis of the significance of the effects of the different drugs*

Effects from	*Drug administered*	*Chi square test (groups according to drug thought taken)*	*Result*
Caffeine			$p < 0.01$
Thiopropazate	Caffeine	Stimulating vs. relaxant and sleep-inducing	Striking
Secobarbital			Striking
Caffeine			Striking
Thiopropazate	Thiopropazate	Relaxant and sleep-inducing vs. stimulating and inactive	$p < 0.001$
Secobarbital			$p < 0.001$
Caffeine			Not applicable
Thiopropazate	Secobarbital	Sleep-inducing and relaxant vs. stimulating and inactive	$p < 0.01$
Secobarbital			Striking

The chi square test has been used to compare, where applicable, the numbers of high and low scorers in the subjects grouped according to the drugs which they thought they had received.

ported that they had had the effects associated with the drug which they thought they had received. The distribution of the guesses for the four possible drugs, after an active drug had been received, was compared in the placebo reactors and other subjects. No significant difference was found between them.

Although the subjects were told that they would receive four different drugs, some of them stated that they had received the same drug more than once. After receiving the first drug, the subjects could have decided which drug they received on each occasion by a combination of elimination and observation of their symptoms. When the subjects stated that they had received the same drug more than once it was clear that they were not using a process of elimination to help them decide which drugs they had received. It was therefore possible to divide the subjects into eliminators and noneliminators by their answers on the forms. Those classified as eliminators, however, were not necessarily *all* eliminators, since some of them may have made all their guesses wholly on the basis of their symptoms, but all those classified as noneliminators were necessarily in this class. The placebo reactors were divided into eliminators and noneliminators on this basis, and their distribution according to the chronologic order in which lactose was administered is shown in Table VI. The numbers of placebo reactors were highest in the first and last sessions. The proportion of eliminators was higher in the last session and lower in the first session. This suggests that a number of apparent placebo reactors reacted in this way because they were merely eliminators. The proportion of noneliminators was higher in the first session and lower in the last session. This suggests that among this group the very fact that the subjects were taking a capsule produced effects. There were insufficient numbers in this group, however, to determine whether there was any correlation between the effects observed and the drug which the subject thought he was receiving.

Table VI. *Analysis of the placebo reactors as eliminators; distribution according to the chronologic order in which lactose was administered*

Group	Session			
	B	*C*	*D*	*E*
Eliminators	3	2	2	7
Noneliminators	5	2	1	3
Total No. of placebo reactors	8	4	3	10

Discussion

This experiment compares the effects of a central nervous system stimulant and a depressant drug with those of a tranquilizer in normal, young, ambulant adults. The actions of these drugs were probably influenced by several factors which were not wholly under experimental control. The subjects were told to have lunch an hour before taking the drugs, but this instruction was not always obeyed. It was clear that the food intake at lunch time varied considerably among the subjects. The rate of absorption of the drugs and the time their effects appeared would be affected by these variations. In ambulant subjects, the depressant action of secobarbital would be less intense than if the subjects were preparing for sleep, although this ought not to have occurred in the case of the tranquilizer. At the time when the psychologic tests were performed, the experimental conditions would tend to diminish the effects of the secobarbital, but 8 or 9 hours later when the subjects were preparing for sleep, its hypnotic effects would have been disappearing. It has been shown that habituation and tolerance to caffeine occur in the normal adult population.[6, 7] It is possible that these phenomena may have been present in a proportion of the experimental subjects, and for this reason, the caffeine may have been less effective in

some of the subjects. The time for carrying out the psychologic tests was chosen because these drugs are believed to be exerting their pharmacologic effects 2 hours after administration. However, individual variations in their rate of absorption and in the subjects' central nervous system excitability probably affected considerably the intensity of their responses to the drugs in the psychologic tests. The subjective observations during the whole 18 hour period were thus probably of more significance than the objective measurements performed for a few minutes after 2 hours. Therapeutic doses of all the drugs were employed, but, as Wolf[18] has pointed out, responses to the administration of drugs are greatly affected by the environmental conditions as well as by intraindividual variations. The effects of the drugs as reported by the subjects may be influenced by these factors, but the responses, characteristic of the actions of the different drugs which were selected from the forms, suggest that in spite of these disturbing factors the drugs were, in general, producing pronounced pharmacologic actions.

The subjects stated that the pharmacologic effects of thiopropazate closely resembled those of secobarbital in spite of the fact that the conditions of the experiment tended to diminish the intensity of action of secobarbital. Both drugs caused drowsiness and relaxation. The subjects said that they did not wish to receive either of them again, presumably because they did not like the depressant effects which were produced on normal daytime activities. Although there were resemblances between thiopropazate and secobarbital in hypnotic effects, it was possible to differentiate between them by the effects which the subjects reported on the forms. Thiopropazate did not cause blurred vision or dizziness as did secobarbital. The feeling of alertness produced by caffeine was preferable to the central nervous system depression caused by the other drugs. This effect was not outweighed by the sleeplessness which occurred in a proportion of the subjects during the following night. So pronounced were the pleasant effects of caffeine that some of the subjects would positively have liked to receive it again.

It was found that a definite association occurred between the effects attributable to the drugs and the subjects' impressions about which drugs they had received. The fact that the subjects knew which drugs they would receive but did not know their order gave an opportunity for the subjects to react positively whether they had received the drugs or not. The degree of reaction of the subjects would depend upon their degrees of suggestibility to their own impressions. The experimental results indicate that if the subjects guessed correctly which drug they had received, they responded to it vigorously. If, on the other hand, they guessed that they had received a depressant drug when they had in fact received caffeine, or vice versa, the effects of the drug were partially or completely inhibited. Not only could pharmacologic actions be inhibited in this way, but a false assumption about the identity of a drug produced effects which could be attributed to the action of the drug which the subject thought he had received rather than to the action of the drug which he had actually had. These observations are in agreement with those of Lasagna and colleagues,[13] who, in a study of the placebo response, reported a higher incidence of relief from morphine in those who reacted positively to placebos than in those who did not. Beecher[1, 2] suggested that this supports the hypothesis that the more suggestible the subject, the greater the relief not only from a placebo but also from an active drug. The present experimental results provide evidence which support this hypothesis. If a drug is administered and a description of its effect is given to the recipient, it can be anticipated that the effect will be more pronounced than if the description is not given. Similarly, some degree of inhibition or variation in the drug's action can be anticipated if a false description of its action is given.

The definition of a placebo reactor in these experiments as a subject who stated that he had received an active drug when he had in fact received lactose was based on the assumption that the subjects made this statement only when they observed pharmacodynamic effects attributable to one of the active drugs. Any of the placebo reactors who carried out the experiment by a process of elimination clearly were not true placebo reactors by this definition. However, even these subjects had to observe the pharmacodynamic effects in the early stages of the experiment before they could use the eliminative process. The proportion of placebo reactors was within the range reported by other workers.[2] Larger numbers of the placebo reactors thought they had received the stimulating or relaxant drug than the sleep-inducing drug. When a subject stated that he had received the stimulating drug, he suffered from effects attributable to *caffeine* more markedly than to either of the other drugs. Similarly, when it was thought that either of the depressant drugs had been received, their effects were more pronounced than those attributable to *caffeine*. The proportion of noneliminators among the placebo reactors was highest in the first experimental session. This confirms the suggestion that the taking of a capsule has the property in certain individuals of producing appropriate effects, since in this session the eliminative process could not have been used at all. It is possible that the first drug-taking session was associated with more stress than the subsequent sessions in these individuals. Beecher[1] has shown that in situations where the stress component is greatest, placebos are most effective. It would therefore be expected that the most pronounced effects among the placebo reactors would occur in the earlier sessions, before they had become accustomed to the experimental procedure.

Conclusions

1. The responses of normal volunteers to the action of stimulant, depressant, and tranquilizing drugs on the central nervous system and to a placebo can be assessed quantitatively by examination of their answers to questions about the effects of the drugs.

2. The subjects were informed about the actions of the drugs they were going to receive but were not told the order of administration. By asking the subjects to give their opinions about which drug they had received after its pharmacologic action had occurred, the relationship between the action of the drug on the subject and the effect of the suggestibility of the subject on the action of the drug was assessed. This also gave the subject an opportunity to react to a placebo.

3. When the subjects guessed correctly which drug they had received, they responded to it vigorously. When they guessed incorrectly, the effects of the drug were partially or completely inhibited. This provides experimental evidence for the well-known therapeutic observation that if a drug is administered and a description of its effect is given to the recipient, it can be anticipated that the effect will be more pronounced than if the description is not given.

4. The number of placebo reactors, defined as the subjects who guessed that they had had an active drug when they had actually received the placebo, was within the usual range. The placebo reactors reported that they suffered from the effects usually associated with the drug they thought they had received and not from either of the other drugs. The effects attributed to the placebo were most pronounced in the first drug-taking session in some of the subjects; this is related to the stress which may have been associated with this session in these particular subjects.

5. The subjects preferred the effects of caffeine to those of the tranquilizer thiopropazate or those of secobarbital (quinalbarbitone). The effects of thiopropazate could be distinguished from those of secobarbital with difficulty by the subjects.

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Effect of methionine sulfoximine in man

Flour bleached with nitrogen trichloride (agene) has been known to cause canine hysteria or "running fits" in dogs and other animals but not in man. Methionine sulfoximine, the active toxic material in flour so treated, was shown in this study to produce toxic psychosis in man, associated in one instance with reversible electroencephalographic changes. The toxicity of methionine sulfoximine was prevented in 1 subject by the simultaneous administration of large doses of methionine.

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In 1946, Mellanby[4] noted that wheat flour bleached with nitrogen trichloride (agene) when fed to dogs produced "running fits" or canine hysteria. This was confirmed by other workers[6, 12] in dogs, cats, monkeys, and rats. In 1950, the toxic substance in "agenized" flour was identified as methionine sulfoximine, an analogue of the naturally occurring amino acid methionine, and was synthesized by Misani and Reiner.[5]

Because of its structural resemblance to other amino acid analogues which have been effective against various animal tumors, the effect of methionine sulfoximine on the growth of sarcoma 180 in mice was studied by Clarke, Reilly, and Stock.[1] The compound was found to be ineffective as a tumor inhibitor when used alone but did appear to potentiate the tumor-inhibitory activity of the glutamine antagonists O-diazoacetyl-L-serine (azaserine) and 6-diazo-5-oxo-L-norleucine (DON).

Detailed pharmacologic studies of methionine sulfoximine and DON in rats, mice, and dogs by Philips* revealed pathologic, biochemical, and hematologic changes similar to those produced by DON alone, and the only toxic effects of methionine sulfoximine appeared to be on the central nervous system. Because of its possible usefulness in clinical cancer chemotherapy, an evaluation of its effects in man was undertaken.

Material and methods

DL-Methionine-DL-sulfoximine is a white powder. It was given orally in capsules to the 7 hospitalized patients with far-advanced, nonresectable cancer described in Table I. The material was given in divided

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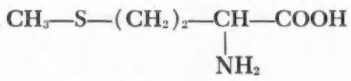
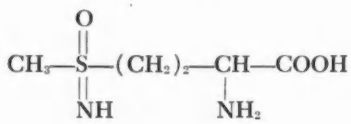


Methionine



Methionine sulfoximine

doses every 6 or 8 hours. In protection studies, DL-methionine was given by mouth, in tablets, also in divided doses. The dosages for each drug are given in Table I.

Each patient was given a general hospital diet. Prior to administration of the compound, laboratory evaluations of hepatic, renal, and hematologic status were made. These were repeated at regular intervals during the period of observation. Each patient was observed closely for evidence of tumor regression, measurable in each case either roentgenographically or by direct observation of tumor masses.

Results

There were no changes in hepatic or renal function or in hematologic status and no evidence of tumor regression in any patient.

The effects of methionine sulfoximine were limited to the central nervous system. Four patients manifested frank hallucinations, disorientation, and marked agitation which continued for from 1 to 3 days after administration of the compound was stopped. The onset of these abnormalities appeared to be related principally to the size of the daily dose rather than directly to the cumulative dose. Thus, a dose of 200 to 400 mg. daily produced toxic psychoses in 3 to 5 days, whereas smaller doses could be given for much longer periods of time without evidence of toxicity. The onset of frank psychosis was usually preceded by 1 to 2 days of restlessness and apprehension. The mental state cleared without the addition of methionine. After return to a normal mental state, the patients remembered, and had insight into, their abnormal behavior.

The largest course of methionine sulfoximine was given to the patient with carcinoma of the cervix; it was administered in combination with methionine at a minimum methionine:methionine sulfoximine ratio of 19:1 (Table I). This produced no neurologic or psychologic abnormalities, and an electroencephalogram made during this period was normal (Fig. 1). Readministration of methionine sulfoximine alone in smaller doses produced hallucinations, disorientation, and agitation. A lumbar puncture performed in this patient a few hours after the onset of psychosis revealed no abnormalities of cerebrospinal fluid composition or dynamics. An electroencephalogram made during the psychotic episode was technically unsatisfactory. Therefore, after she had recovered completely, methionine sulfoximine was readministered for 3 days at a lower dose, without clinical evidence of toxicity. An electroencephalogram recorded at that time was abnormal, with activity suggestive of organic brain damage (Fig. 2). Serial electroencephalograms obtained during the posttreatment period showed a gradual return toward normal during the next 2 weeks.

The patient with Ewing sarcoma did not develop psychosis with the administration of methionine sulfoximine but became extremely lethargic, progressing to semicoma. Withdrawal of the drug was promptly followed by return to an alert, cooperative state. Readministration in the same dosage failed to produce the lethargy previously seen, and the patient died of pulmonary metastases before drug toxicity was reproduced.

In the patient with carcinoma of the lung who received methionine sulfoximine in combination with DON, mental aberrations developed which regressed only partially after the administration of the two compounds was stopped. He subsequently developed a severe peripheral neuropathy which persisted until his death from metastatic cancer. Examination of the cerebro-

spinal fluid and autopsy examination of the central nervous system failed to reveal the cause of the mental and neurologic abnormalities. In this single instance, the possibility cannot be excluded that methionine sulfoximine together with DON produced irreversible functional changes in the central nervous system.

Discussion

The ability of methionine sulfoximine to produce "running fits" in dogs and similar phenomena in cats, monkeys, and rats has been well established.[4, 6, 12] Quantitative differences in susceptibility were noted between the different species. Species differences in the ability of methionine to protect animals from the toxicity of methionine sulfoximine also were described by Gershoff and Elvehjem,[2] who found that when methionine was given in a dose 100 times that of methionine sulfoximine, dogs were protected from otherwise lethal doses of methionine sulfoximine. A ratio of only 9:1 of methionine:methionine sulfoximine was required to protect monkeys.

Newell and associates[7] were unable to produce psychologic or neurologic abnormalities in man with 100 Gm. daily of agenized flour. However, since the maximum conversion of methionine to methionine sulfoximine by this process is about 5 per cent,[2] it is apparent that their subjects received an average of only 7 mg. daily of methionine sulfoximine in combination with about 19 times that amount of methionine. Even if the entire caloric intake had been in the form of agenized flour, the daily dose of methionine sulfoximine would have been only about 65 mg. together with about 1.3 Gm. of methionine. The present study suggests that this approximates a protective ratio for man. In other species, e.g., dogs, which are more sensitive to

Table I. *Doses and effects of methionine sulfoximine in man*

Age of patient	*Sex*	*Diagnosis*	*Maximum daily dose* (mg.)*	*Total dose (mg.)*	*Other medication*	*Response*
41	F	Carcinoma of cervix	400× 4 days	5,800	Methionine 6-7.5 Gm per day	None
			200× 3 days	900		None
			300× 3 days	1,400		Agitation, disorientation, hallucinations
			200× 2 days	500		EEG changes
54	F	Carcinoma of breast	300× 5 days	3,300		Anxiousness, restlessness
			300× 2 days	700		Agitation, disorientation, hallucinations
42	F	Carcinoma of ovary	400× 1 day†	3,075		Hallucinations, lucid intervals
30	F	Malignant synovioma	150× 3 days	1,690		Disorientation, hallucinations
17	M	Ewing sarcoma	300× 2 days	2,200		Marked lethargy
			300× 8 days	2,400		None
45	M	Carcinoma of lung	100× 3 days	1,425	DON, 2.5 mg. per day	Disorientation, hallucinations (see text)
65	F	Carcinoma of ovary	10	71		None

*DL-Methionine-DL-sulfoximine.

†Brief but definite hallucinations began on the third day at 200 mg. per day.

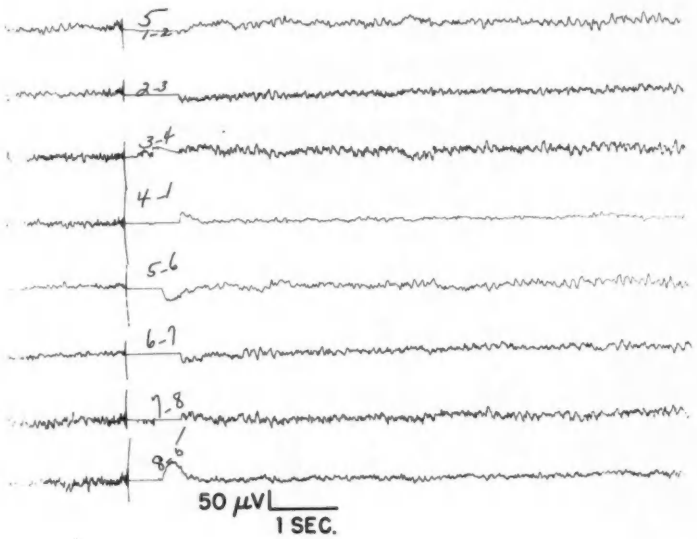


Fig. 1. Electroencephalogram of the patient with carcinoma of the cervix during administration of methionine and methionine sulfoximine. The tracing is normal.

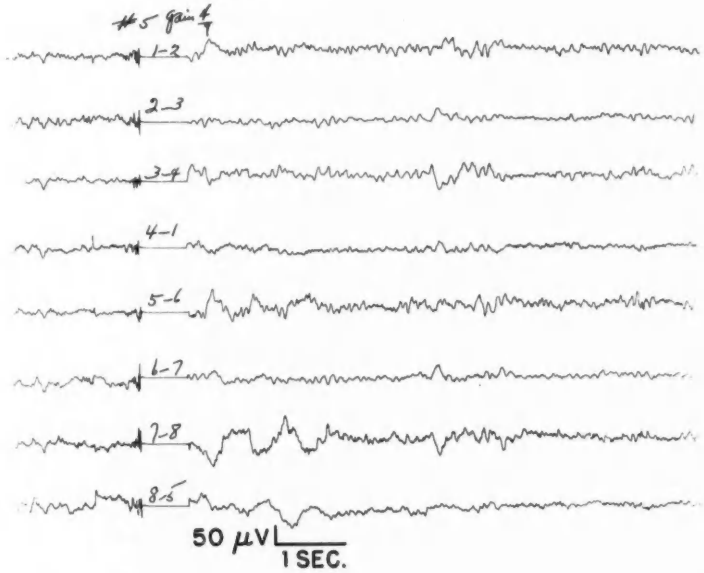


Fig. 2. Electroencephalogram during administration of methionine sulfoximine alone to the patient with carcinoma of the cervix (see text). The tracing is diffusely abnormal, with prominent slow activity, most marked in the left temporal region.

methionine sulfoximine and in which a higher methionine:methionine sulfoximine ratio is necessary for protection, agenized flour has produced neurologic and behavioral abnormalitics. The production of neurologic abnormalities in man by crystalline methionine sulfoximine indicates a susceptibility of man which parallels that of dogs, monkeys, and rodents. The convulsions seen in animals did not occur in man. This difference is probably a result of the fact that the onset of psychosis in man led to withdrawal of the toxic agent. It is posssible that if administration of methionine sulfoximine had been continued, convulsions would have been seen. Observation of dogs* given methionine sulfoximine has revealed a change in behavior prior to the onset of convulsions, with increased restlessness, aimless barking, and staring. These may be interpreted as preconvulsive hallucinations and possibly psychosis although precise behavioral studies have not been performed on dogs in this state.

DL-Ethionine, another analogue of methionine, was given by White and Shimkin[15] to 6 patients with advanced cancer

*F. S. Philips: Personal communication.

in doses of 0.6 to 45 Gm. daily. Toxicity occurred in 5. The most prominent feature of ethionine toxicity was psychosis. In addition, there were impairment of liver function, proteinuria and hematuria, dermatitis, diarrhea, and in some patients leukopenia and thrombocytopenia. The toxic effects were minimized when patients received diets that contained adequate methionine and apparently could be reversed by methionine given early after the onset of toxic symptoms.

The precise mechanism by which the methionine analogues produce their toxic effects is not known. Simpson, Farber, and Tarver[13] showed that ethionine inhibited the incorporation of isotope-labeled methionine and glycine into proteins and concluded that it acted by inhibiting protein synthesis. Other studies[3, 14] have shown that ethionine is de-ethylated and the ethyl group incorporated into protein, probably by participating in transmethylation reactions, resulting in an abnormal protein which is functionally inadequate. Rabinovitz, Olson, and Greenberg[11] have shown that in Ehrlich ascites cells in vitro, ethionine is incorporated into protein and inhibits the incorporation of methionine. The two amino acids are competitive in that system, and the affinity of ethionine for incorporation is about 1/600 that of methionine.

Methionine sulfoximine appears to inhibit the incorporation of other amino acids into protein,[9] and this inhibition is prevented by glutamine. The synthesis of glutamine from glutamate and the transfer of glutamyl groups have been shown to be inhibited by methionine sulfoximine.[8, 10] It is not known whether its relationship to glutamine is responsible for the neurotoxicity of methionine sulfoximine or for its potentiation of the tumor-inhibitory effects of the glutamine antagonists azaserine and DON.

The effects of methionine sulfoximine and ethionine in man are not identical. Although psychosis has been produced in man by both compounds, the distinct impairment of liver function and the renal, dermatologic, and hematologic abnormalities seen with ethionine did not occur with methionine sulfoximine. Information is not now available to indicate whether the clinical differences are due to differences in mechanism of action of the two compounds or to differences in side effects which may not be related to influences on protein synthesis.

In mice, ethionine is less toxic than methionine sulfoximine, i.e., it is tolerated at a larger dose, and when used at the maximum tolerated dose in combination with DON or azaserine, it produced less enhancement of antitumor activity than did methionine sulfoximine at the maximum tolerated dose, although some degree of potentiation was apparent.*

In contrast to its effects on sarcoma 180 in mice, DON alone has not been found to affect tumor growth in man. The single case cited here does not indicate whether tumor regression in man may occur with the combination of DON and methionine sulfoximine or if there is additive or synergistic toxicity. Further studies of combinations of amino acid analogues may be useful in clarifying their relationships and mechanisms of action.

The author is grateful to Drs. Gerald Klingon and Donald Simons for interpreting and reviewing the electroencephalograms.

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Method for evaluating antipruritic agents

Studies on methdilazine

Pruritus, a common complaint, is a most difficult symptom to evaluate and is altogether analogous to pain in this respect. A method for evaluating the antipruritic activity of drugs is described which makes use of the reaction produced by urushiol. A skin lesion is created in healthy volunteers sensitive to poison ivy by application of a diluted solution of urushiol. The fully developed lesion produces severe itching, and the response of the subject can be studied by the standard double blind technique for the antipruritic effect of a drug compared with that of placebo. The lesion continues uniform in intensity for a period long enough to permit the subjects to serve as their own controls.

In this technique, methdilazine and trimeprazine were compared to a placebo. Both drugs showed antipruritic efficacy, methdilazine producing a better response than trimeprazine under the conditions of the evaluation.

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Pruritus is one of the most common and, at times, most resistant symptoms in man. Although the value of some of the antihistamines, phenothiazines, and steroid hormones has been amply demonstrated, more potent agents are needed.

There are many agents which have an antipruritic potential, but it is most difficult to assess properly their merit in man. This is necessarily so because of the inherent nature of pruritus itself, which is known to vary not only from individual to individual but in the same individual under different situations. It is altogether analogous to pain; therefore, any study involving pruritus is subject to the same hazards as would be concomitant in a study of pain. It is consequently essential that any evaluation of antipruritic agents be as objective as possible. Obviously, fleeting or short lasting pruritus is not suitable, neither is a type which changes readily in intensity or creates an emotional overlay.

After experiencing a bout of poison ivy, it occurred to me that this dermatitis, if properly controlled, might provide an excellent means for producing a long-lasting, intensely pruritic lesion which would be well known and would consequently not create an emotional overlay. It would have the further advantage that it could be followed carefully and photographed for permanent recording. In addition, the lesion and the pruritus would be of sufficient

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duration to permit studies of up to 48 hours for three different agents, and the patient could therefore serve as his own control. Although this lesion represents only one type of itch and, of course, could not be considered as typical of all itch patterns, it nevertheless is useful if this limitation is borne in mind.

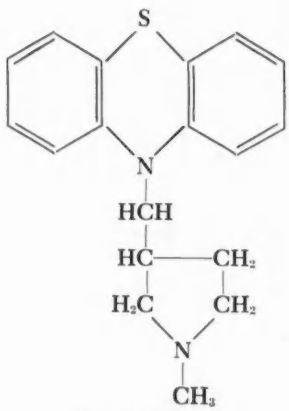
It was decided to employ this technique in the study of a new antiallergic agent, methdilazine hydrochloride.* Trimeprazine,† which has been observed to have strong antipruritic properties in certain states, and a placebo were used to ascertain the relative antipruritic potency of methdilazine. The technique employed by Thurmon, Ottenstein, and Bessman[9] in their study of the effect of agents on the activity of urushiol was followed.

Methdilazine is a long-acting antihistamine of the phenothiazine series.

Quantitative pharmacologic tests in animals have shown methdilazine to be a potent antihistamine with long duration of effect. There is animal experimental evidence, as well as clinical evidence in man, that it also possesses anti-inflammatory properties. It is effective in preventing pulmonary edema induced in rats by injection of ammonium chloride. Cardiovascular collapse induced in cats by the endotoxins of *Escherichia coli* is also prevented by methdilazine. It actively inhibits increased capillary permeability and edema formation when these are induced by such agents as yeast, dextran, egg white, or serotonin.[7]

Methdilazine is not a tranquilizer and does not exhibit, to any extent, an effect on conditioned responses. In this it differs from many phenothiazines. However, it does potentiate the action of barbiturates, alcohol, and narcotic analgesic drugs.[5, 7] It does not, even in high doses, exert any untoward effect on the electroencephalogram.

Animal studies show that methdilazine is rapidly and completely absorbed from the gastrointestinal tract and, after absorption, promptly leaves the blood stream. It has a long duration of action, and an antihistaminic effect may persist for 12 hours after a single oral dose. Elimination studies have shown it to be removed rapidly enough so that repeated daily doses do not lead to accumulation.[11]



Methdilazine

Clinical trials have shown that very large doses, in the order of 50 to 75 mg. daily, can be given to elderly patients for 6 weeks without the appearance of any toxic effect clinically, chemically, or hematologically. The dose usually recommended is 4 to 8 mg. two to four times daily.

Methdilazine has been studied in large numbers of patients for its effect in the treatment of nasal allergies, bronchial asthma, allergic dermatoses, and pruritus, with clinical results which compare favorably with the potent antihistamines. The only toxic effects noticed in clinical trials were drowsiness, dry mouth, constipation, headache, vertigo, and irritability; drowsiness was by far the most common complaint, and it occurred in less than 10 per cent of the individuals studied.[1, 3, 4, 6, 8, 10]

Method

Urushiol, the active principle of the poison ivy plant, was diluted to make a 0.01 per cent solution in 70 per cent alcohol. Squares ½ inch in diameter of Whatman No. 42 filter paper were saturated with the diluted urushiol solution and then placed

*Tacaryl.

†Temaril.

on the flexor surface of the forearm about 3 inches from the fold of the elbow. The papers were fastened down with cellophane or adhesive tape and left in place for 2 hours, after which time the patches were removed. The arm was then thoroughly washed by lathering with soap and rinsing with water. This was repeated at least six times in order to remove completely any unattached urushiol.

The 11 subjects were volunteers with a history of sensitivity to the poison ivy plant. Most were younger individuals who had previously experienced several bouts of poison ivy dermatitis, with the latest attack in recent years.

In approximately 24 hours, the lesion appears as a faint, erythematous, slightly elevated square patch, beginning to itch (Fig. 1). There should be absolutely no spreading from the site of the original patch application. At the end of 48 hours, the lesion is usually of full intensity, very erythematous, itching severely, with edema and beginning vesiculation. The lesion, as now established, almost invariably continues for approximately 6 more days, after which it loses its inflammatory character and the pruritus decreases. Crusting with scaling occurs, followed by complete healing. In some individuals, the skin at the site may retain a faint brown pigmentation for several weeks.

When the lesion was firmly established, usually in 48 hours, the subject was considered ready for the study to begin. Neither the subject nor the physician observing the lesion and recording the subject's experiences knew which drug was being used at any time. The active drugs in their most commonly employed clinical doses (methdilazine, 8 mg.; trimeprazine, 5 mg.) and the placebo, consisting of lactose, were in red gelatin capsules of identical appearance, and a code was assigned to each box of six capsules. The subjects were instructed to take one capsule after meals and to continue this for 2 days. They were then given a second box of capsules for the next 2 days and a third box for the last 2 days. Treatment was randomized. During the period of medication, the subjects were instructed to keep a careful record of the intensity of the itching, how often they were aware of it, and whether they were awakened by it at night. They were also asked to observe the character of the lesion, such as swelling, erythema, vesiculation, exudation, bullae formation, and induration. In addition, they were to note any untoward effects, such as drowsiness, slowing down, excitement, and insomnia, or any changes in their normal reactions. Subjects were seen daily by a physician. At 2 day intervals, color photographs were taken of the lesions.

In order to check the anti-inflammatory activity of methdilazine, a lesion was created by urushiol on the other forearm after the first lesion had healed. The subjects were then given 8 mg. of methdilazine after meals daily until this second lesion was free of all pruritus, erythema, and induration and was healing satisfactorily. The previous lesion served as a partial control only, because methdilazine and trimeprazine had been administered 2 days each.

Results

The results of this study are given in Table I. It is apparent, when studied by this method, that methdilazine exerted a potent antipruritic effect. Of the 11 subjects, 6 had complete and 3 had partial relief from pruritus. Two of the volunteers were afforded no relief, and 1 of these felt

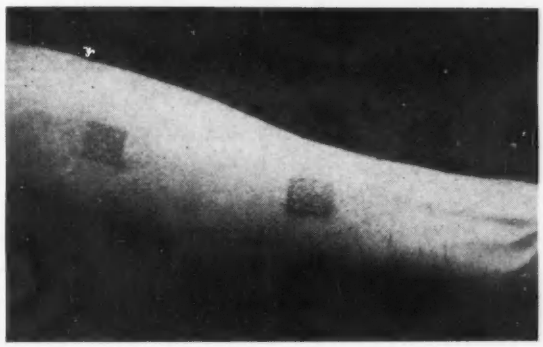


Fig. 1. Urushiol reaction.

Table I

Age of patient	Sex	Pruritus severity*			Duration of inflammation from first appearance (days)		Remarks
		Trimeprazine	Placebo	Methdilazine	Control	Methdilazine	
26	F	++	++	+	7	6	
27	F	++	++	0	7	8	Sedation caused by methdilazine
25	M	+–	+++	+	6	7	
23	M	0	0	+++	6	6	Believed methdilazine increased itching
23	F	0	++	++			
34	F	++	++	0	7	5	Sedation caused by methdilazine
23	F	0	0	0	6	6	Controlled itching with methdilazine
27	M	++	++	0	6	6	Sedation caused by methdilazine
53	M	++	+++	0	7	7	Sedation caused by methdilazine
35	M	++	++	+	7	7	
50	M	++	+++	0	7	7	

*Degree of pruritus is indicated on a scale increasing from 0 to ++++.

that the itching was intensified by the use of the drug. Four persons complained of sedation and felt that the dose would have to be reduced if they were to continue taking the drug for very long. This sedating action must contribute significantly to enhancing the antipruritic effect of this agent.

Trimeprazine gave complete or nearly complete relief from pruritus in 4 subjects. It afforded partial relief in 7. No untoward effects were observed. Under the conditions of this experiment, trimeprazine did not appear to be as effective an antipruritic agent as methdilazine. This result may be related to the doses compared, or it may be of a more fundamental nature, involving a lack of antihistaminic or anti-inflammatory action or significantly less sedative effect than that of methdilazine.

The placebo provided complete relief for 2 subjects, partial relief in 6, and none in 3. Although these results are inferior to those of methdilazine and trimeprazine, they indicate the difficulties inherent in attempting to evaluate the antipruritic properties of drugs.

Methdilazine exerted no striking effect on the length, severity, or speed of healing of the urushiol lesion over that observed in the controls. However, the relief of itching made the lesions more bearable. More accurate evaluation of this phase of methdilazine activity should be made.

Discussion

Although pruritus is relieved in some respects by many centrally acting drugs, such as the barbiturates, antihistamines, and certain of the phenothiazines, there is as yet no concrete understanding of how they produce this effect. There seems to be little doubt that there is an important central mechanism in pruritus. Nervous tension states associated with rectal, vulvar, or more generalized pruritus, as well as the pruritus often seen after narcotic drug medication, all point to the central origin of pruritus in many situations. Many believe a drug must exert a depressant effect in the hypothalamic area in order to exhibit antipruritic action. Some observers believe pruritus to be in the same category as pain and consider the difference between the two to be only a matter of degree and type of nerves involved. Certainly, it is reasonable to believe that ultimately the most effective approach to the control of pruritus will be by way of the central nervous system.

Although the first phenothiazine compounds, such as chlorpromazine and prochloperazine, showed modest antipruritic action, they are not nearly as potent in this respect as trimeprazine and methdilazine, indicating that changes in molecular structure are important in making these drugs more selective against this symptom. It should be noted that enhanced antipruritic activity appears to be associated with an actual decrease in tranquilizing effect and loss of action on conditioned reflex activity. Furthermore, it is interesting to note that the phenothiazine ring is much less important in this antipruritic effect than are modifications in the side chain. The pyrrolidyl ring which appears in methdilazine and the side chain which is found in trimeprazine when attached to the phenothiazine ring create antipruritic molecules. It is reasonable to suppose that there are many other possibilities in this relationship, and certainly other, even more potent antipruritic agents will be found if this field is carefully explored.

Conclusions

1. Urushiol, the active principle of the poison ivy plant, can be used to create a standard, long-lasting, repeatable pruritic lesion which readily lends itself to the study of antipruritic agents.

2. Methdilazine has been shown to exert an effective antipruritic effect in volunteers experiencing pruritus from the active principle of poison ivy.

3. Synthesis of new phenothiazines with variations in the side chain should lead to the development of new and perhaps more effective antipruritic agents.

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Clinical and experimental observations with methiodal, an absorbable myelographic contrast agent

The intrathecal injection of methiodal in myelography is associated with spinal anesthesia, pain, and autonomic dysfunction. Experiments carried out in cats revealed that methiodal blocked conduction in the ventral and dorsal route fibers, an action which did not develop in peripheral nerves. Other experiments in cats indicated that the duration of the effects on conduction is a consequence of slow removal of the drug rather than of delayed recovery. The results of these experiments are taken to indicate that the effects of methiodal may be ascribed to an action on the spinal cord or nerve roots.

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In 1931, Arnell[1] introduced methiodal sodium (sodium monoiodomethane sulfonate) for use in myelographic examination. During the past 20 years, methiodal became more generally accepted for this purpose, first in Scandinavia and later in other European countries. This compound provides excellent x-ray contrast, filling the intrathecal space in great detail. Absorption from the intrathecal space proceeds at such a rate that about 30 minutes after injection, x-ray differentiation is no longer possible.[7] The renal excretion of intravenously administered methiodal has been established.[2]

This report presents observations on the use of a buffered 20 per cent solution of methiodal.*

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*Abrodil, Kontrast U, Skiodan.

Procedure for intrathecal injection

Following Arnell's recommendations,[1] patients are placed in the lateral decubitus position on a flat surface tilted about 15 to 20 degrees so that the cephalad portion is elevated above the caudal area and the spine remains straight. After lumbar puncture, 12 to 15 mg. of tetracaine mixed with spinal fluid (0.1 ml. per 1 mg. of tetracaine) is slowly injected. There is negligible peripheral anesthesia. After subsequent injection of 10 ml. of contrast medium, x-rays are taken while tilting the patient from lateral decubitus to prone position. This procedure results in outline of only one side of the intrathecal space in the lower lumbar area. Through personal communications, we have learned that others have been producing myelograms with excellent outline of the entire lumbar area with buffered methiodal by maintaining the

patient in a sitting position and inserting 20 ml. of contrast medium.

Clinical observations

This report covers observations in forty-two myelographic studies using buffered methiodal. The most consistent untoward effect after intrathecal injection of the medium was a rapid increase of the degree of spinal anesthesia, exceeding that obtained with the preceding dose of tetracaine. About 30 minutes later, it was common to find the level of spinal anesthesia somewhere between upper thigh and umbilicus, usually about the inguinal crease.

Seven patients described back pain similar to the original complaint for which myelography was performed but stated that it was more severe. Six patients complained of leg pain which, in 4 patients, was also similar to the original complaint. One patient complained of a prickly sensation in the legs which accompanied the return of sensation after anesthesia. Another patient complained of a feeling of pressure in the feet during recovery from anesthesia. This sensation disappeared after 15 minutes. Three patients complained of pain definitely localized to the rectum.

One patient had received only 10 mg. of tetracaine. About 90 minutes after the intrathecal injection, all sensation had returned and he described an acute, severe, burning pain in the rectum. To relieve this symptom, which was quite unbearable, the patient had to be given a narcotic analgesic. Two hours later, the pain was completely relieved and no residual symptoms could be observed.

Eleven patients complained of headache which did not seem different from those after lumbar puncture. In 8 patients, there was nausea and vomiting which might have been due to the spinal puncture per se. Ten patients had some ill-defined complaints, chiefly headache, for 24 hours. There were 3 patients in whom symptoms lasted more than 24 hours, a patient with meningism that lasted for 2 days, a patient with slowing of urination for 3 days (which could possibly have been due to an enlarged prostate), and a patient who complained for 7 days of a lack of sensation in the rectum (although he responded to pinprick and had normal bowel movements, he stated that he did not feel as if he needed to have a bowel movement).

In 1 patient, there was a fall in blood pressure to a level of 90/60 2 hours after the myelographic procedures. A solution of 5 per cent dextrose and water was then slowly infused, and the pressure quickly returned to normal levels. In this case, sensation and motion were returning to the lower extremities at the time the fall in blood pressure was recorded.

Table I summarizes the effects encountered in the present series.

Lindbloom[4] reported on 54 patients with untoward effects among 700 patients who underwent myelography with buffered methiodal. His list of complaints includes 9 instances of lumbar pain during or soon after injection of the contrast medium and hyperesthesia and leg spasm in 4 cases. Paralysis of leg and sphincter muscles was observed in 9 patients for periods of weeks, but in these cases concentrations higher than 20 per cent were used. Headaches and circulatory disturbances were reported in a large number of instances.

Monroe[6] reported results on the use of buffered methiodal for myelography.

Table I

Effect	*No. of patients*
Spinal anesthesia	42
Back pain	7
Leg pain	6
Rectal pain	3
Headache	21
Nausea	8
Drop in blood pressure	1
Complaints persisting 24 hours or longer	
Meningism	1
Slow urination	1
Poor sensation in rectum (subjective only)	1

Neither the concentration used nor his procedure was described, but untoward effects occurred after 23 of 125 administrations, an incidence of 18 per cent. These incidents were distributed as follows: bladder paralysis 4; rectal paralysis, 4; persistent sacral anesthesia, 2; severe generalized reactions (vascular hypotension, visceral paralysis, fainting, sweating, and collapse), 4; generalized convulsions, 2; and thrombosed caudal vein, 1.

While many of the reactions to intrathecally injected buffered methiodal may be labeled "unspecific" and consequent to spinal puncture as such, two general features emerge from the cumulative clinical experience which appear specifically attributable to this agent: (1) spinal anesthesia exceeding in intensity and level that caused by the slightly effective dose of tetracaine administered prior to intrathecal injection of the medium and (2) the appearance of pain or prickly sensations projected into the back, leg, or rectum. The latter appears commonly after 1 to 2 hours and, therefore, at a time when elimination of the local anesthetic is presumably complete. It may be noted that Arnell's[1] original procedure involved prior administration of a local anesthetic to mitigate or prevent initial pain with injection of buffered methiodal.

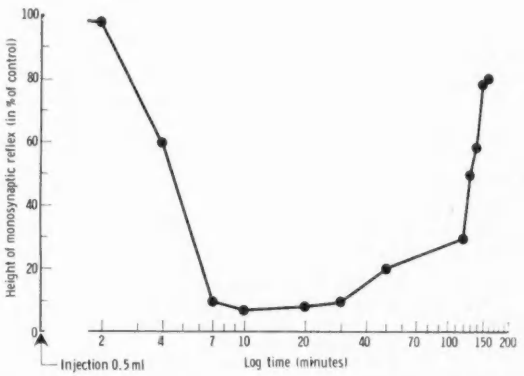


Fig. 1. Height of a monosynaptic reflex response in relation to time after intrathecal injection of 0.5 ml. buffered methiodal (cat under chloralose anesthesia).

Experimental observations

Experiments were performed on cats to examine the nature of the actions of buffered methiodal on neural structures to which the reactions observed in the clinic may be attributed. There were three types of experiments.

Effect of buffered methiodal on exposed ventral and dorsal root fibers in situ. This procedure involved the application of single electrical stimuli to the exposed sciatic nerve and the recording of the incoming volley in a dorsal root and of the ensuing reflex activity in a ventral root filament of L7. In cats under chloralose anesthesia, the spinal cord was exposed by laminectomy extending from L5 to the lumbrosacral joint. The exposed cord was covered with a temperature-controlled (37° C.) and oxygenated (95 per cent O_2 + 5 per cent CO_2) emulsion of Krebs-Ringer solution in mineral oil. The root filaments selected for recording were severed, the dorsal root bundles centrally from the spinal cord and the ventral root bundle peripherally before its passage through the dura mater. The remaining bulk of ventral and dorsal root L7 remained in continuity with the peripheral and central connections. Under these conditions, the dorsal root spike appeared in the oscilloscope 1.5 to 1.9 milliseconds after the sciatic nerve stimulation in the popliteal fossa. Efferent activity started about 1 millisecond later in the ventral root bundle and continued to a variable degree for 10 to 20 milliseconds, reflecting monosynaptic and polysynaptic reflex discharges, respectively.

Within 3 to 5 minutes, the addition of 0.5 to 1 ml. of buffered methiodal to the mineral oil–Krebs-Ringer solution emulsion pool of 100 to 150 ml. covering the exposed spinal cord almost completely abolished efferent and afferent activity. This effect developed in afferent and efferent fibers at about the same time.

Even when repeated six to eight times over a period of 1 to 2 hours, replacement of the medium-containing mineral oil–Krebs-Ringer solution emulsion by medium-

free emulsion resulted only in incomplete recovery of afferent and reflex activity in the root filaments. The afferent spike did not recover more than 20 per cent of its initial height, and the efferent activity remained similarly curtailed in intensity and duration.

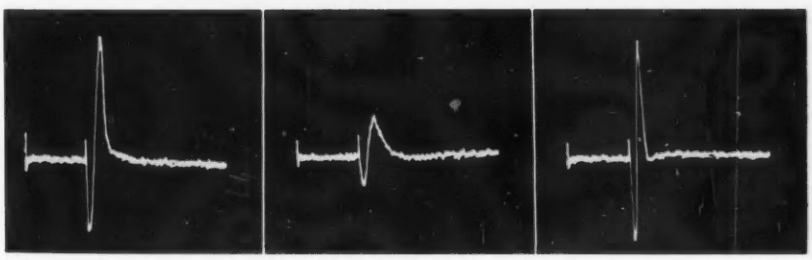
Since the distribution of the medium in the mineral oil–Krebs-Ringer solution emulsion could not be ascertained and since the completeness of its removal from the spinal pool was questionable in spite of repeated changes of the emulsion, these experiments did not permit quantitative estimation of intensity and duration of action. They did, however, indicate a blocking effect on conduction in afferent and possibly also in efferent root fibers. Whether, and to what extent, a blocking action on the fibers and neurons within the spinal cord was involved in the paralysis of reflex activity could not be determined from these experiments.

Effect of buffered methiodal on reflex activity of the spinal cord in situ. To determine this effect, the medium was injected in chloralose-anesthetized cats through a fine polyethylene catheter introduced into the intradural space through a small exposure in one of the upper thoracic segments. The catheter tip was approximately at the L4-L5 level. Reflex activity was tested by recording the reflex discharge in the peroneal or tibial nerve after the application of single square wave pulses of 0.1 millisecond duration to the ipsilateral tibial nerve.[5] The nerves were severed peripherally to the position of the electrodes.

Injection of 0.5 ml. of a 20 per cent solution of buffered medium through the intraspinal polyethylene catheter resulted in abolition of the reflex response. The maximal reflex degression to about 10 per cent of control was attained within 5 to 10 minutes after injection. The recovery curves were determined in four experiments. In the period of 120 to 150 minutes after the injection, the height of the reflex volley attained about 80 per cent of its control value. The reflex response did not further improve during observation periods of up to 4 hours (Fig. 1).

The onset of blocking action on reflex activity was preceded by extension of the hind limb both ipsilaterally and contralaterally to the recording side, by erection of the tail, and by fasciculations of the lumbar muscles. These effects followed immediately after injection and subsided before onset of reflex block.

These experiments substantiate the findings of spinal reflex block by buffered methiodal, reported in the first series of experiments and, in addition, permit an estimate of its duration if the drug administration is similar to the mode of application in clinical use.



A B C

Fig. 2. Compound action potential of S1 ventral root bundle (cat). The stimulating and bipolar recording electrode was located on the root bundle, which was suspended for recording in oxygenated mineral oil–Krebs-Ringer solution emulsion. *A*, Control. *B*, After 3 minutes' exposure to methiodal (0.1 Gm. per 1 ml. of bathing fluid). *C*, Five minutes after exchanging the methiodal-containing solution for Krebs-Ringer solution.

Effect of buffered methiodal on isolated dorsal and ventral root filaments. These experiments were performed to determine whether the time course of action found on intraspinal administration (experiment 2) reflects the kinetics of the removal of the medium from the cerebrospinal fluid or whether it is the consequence of slow recovery of root filaments after removal of the drug. Root filaments of S1 were placed on a pair of recording and stimulating electrodes and, under appropriate precautions, suspended in 15 ml. of temperature-controlled, oxygenated Krebs-Ringer solution, to which the agent was added. For brief periods of stimulating and recording, the electrodes and root filaments were lifted into a layer of mineral oil of equal temperature and oxygenation.

In concentrations of 1 to 2 ml. of 20 per cent buffered methiodal per 15 ml. of Krebs-Ringer solution, the medium reduced the height of the compound action potential by 30 per cent to 50 per cent of the control magnitude. A concentration of 3 ml. of the medium per 15 ml. of Krebs-Ringer solution resulted in complete abolition of conduction within 2 to 4 minutes. After changing to a medium-free Krebs-Ringer solution, conduction was completely restored within 5 to 10 minutes. Further increase of the medium concentration and prolongation of exposure of root filaments to the medium for a period up to 1 hour did not significantly prolong recovery time. Dorsal and ventral root filaments were equally affected by the agent (Fig. 2).

In a few experiments, sciatic nerves were exposed to the medium and similarly tested for conduction of impulses. In concentrations up to twice those affecting root filaments, conduction and excitability were not affected.

Conclusions

A variety of symptoms are encountered in the clinical use of intrathecally injected buffered methiodal (monoiodomethanesulfonate). Of these, spinal anesthesia, sensations of pain, and signs of autonomic dysfunctions appear specifically attributable to an action on spinal cord or roots.

Experiments on cats reveal a blocking action of buffered methiodal on conduction in ventral and dorsal root fibers. This effect is not manifested in peripheral nerves, possibly because the perineurium constitutes a barrier for penetration of the electrically charged methiodal molecules. It appears that the duration of conduction block of root fibers in situ is a consequence of slow removal of the drug from the cerebrospinal fluid rather than a result of delayed recovery after removal of the agent.

The work of Howarth[3] may serve as a basis of comparison: For dibromoprocaine hydrochloride, the rate of disappearance from cerebrospinal fluid after intrathecal injection was measured. The agent could be detected in the cerebrospinal fluid for periods up to approximately 150 minutes. Thus, the kinetics of removal of the medium, as estimated indirectly in these experiments, accords with the directly obtained data for dibromoprocaine hydrochloride.

Apart from the muscular fasciculations and contractions seen immediately after intraspinal injection of methiodal, the present experiments did not reveal signs of excitatory and stimulant effects to which could be attributed the sensations of pain encountered in clinical use.

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Clinical pharmacology of the anti-inflammatory steroids

The physiologic as well as the supraphysiologic manifestations of hydrocortisone and its congeners are reviewed. The effects on metabolic, electrolyte, and tissue systems are considered. These are related to structure and potency of the many congeners of cortisol which have been synthesized. Finally, clinical application to disease is related to basic pharmacologic data.

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Although in contemporary medicine corticosteroids are used principally for their anti-inflammatory effects, these agents have innumerable additional actions which have come to be regarded as "side effects" of therapy. There is a touch of irony in this, inasmuch as the great importance of corticosteroids in facilitating the survival of complex organisms has unquestionably been related to their metabolic effects and not to their anti-inflammatory properties. In actuality, the quantities of corticosteroids normally secreted have very little effect on inflammation. This implies that in order to achieve an anti-inflammatory effect, supraphysiologic quantities of steroids must be given. Metabolic aberrations must, therefore, be expected as inescapable consequences of the use of known corticosteroids as anti-inflammatory agents. To avoid such consequences, new agents must be developed which differ from the natural corticosteroids in being relatively devoid of metabolic activity while retaining anti-inflammatory activity.

The marvelous ubiquity of corticosteroid action deserves mention. There are few physiologic processes which are not influenced, directly or indirectly, by corticosteroids. Yet, so far as we know, these agents do not initiate physiologic processes but merely influence their rates. Apparently, corticosteroids are not consumed in the process of exerting their physiologic effects; in a sense, therefore, they may be regarded as physiologic catalysts.

The anti-inflammatory product of the human adrenal gland is cortisol.* Cortisol is the most potent of the naturally occurring anti-inflammatory steroids. Although cortisone approaches cortisol in anti-inflammatory potency, the former has never been shown to be secreted in significant quantities by the human adrenal gland. There is strong evidence that cortisone as such is not an anti-inflammatory steroid but that it must be converted to cortisol within the body before it can exert anti-inflammatory activity.[47] Of the numerous synthetic corticosteroid derivatives now in use, all are

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*"Cortisol" and "hydrocortisone" are synonymous. Hydrocortisone is the official pharmaceutical designation; cortisol is the term in current usage in the literature on physiology and biochemistry.

closely related to cortisol in chemical configuration.

Numerous recent studies have been concerned with the effects of cortisol on the cellular transport and metabolism of various substances, on the concentration of enzymes in certain tissues, and on the cytology of various tissues; but far too little is known to enable one to say just how the steroid induces these effects. There are still important gaps in our knowledge concerning the connection between these fundamental actions and the clinical effects of cortisol.

There is reason to believe that some of the important biologic effects of corticosteroids represent indirect rather than direct actions. Usually, the effectiveness of a drug is a function of its concentration within the body at a given moment, but with corticosteroids, there is a significant latent period between the time of maximal concentration of the agent in plasma or tissues and the time of maximal effect on blood glucose, electrolyte excretion, or inflammation. Cortisol, for example, disappears with a halftime of a little less than 2 hours. Yet, during the first 2 hours after the administration of cortisol, it is difficult to demonstrate its hyperglycemic effect. But 8 hours after treatment, at a time when most of the cortisol has been metabolized and excreted, the hyperglycemic effect is readily demonstrable.

Manifestations of supraphysiologic levels of cortisol

Alteration of inflammatory responses. Early in the process of inflammation, degenerative changes occur in fibroblasts and mast cells. High concentrations of cortisol within the tissues tend to prevent these degenerative changes.[21] Perhaps it is through this preservation of cellular integrity that cortisol tends to minimize the subsequent exudative and proliferative phases of the inflammatory reaction. Preservation of cellular integrity through the agency of cortisol is also observed in allergic reactions and immune hemolytic disorders. Cortisol suppresses not only the "useless" inflammatory response which is characteristic of many connective tissue disorders but also the "useful" inflammatory response through which the body walls off invading microorganisms. Suppression of useless inflammation constitutes the major indication for the use of cortisol-like steroids in contemporary medicine; suppression of useful inflammation constitutes one of the major undesirable effects of anti-inflammatory steroids.

ACTH suppression. Cortisol indirectly controls adrenocortical secretion by restraining the secretion of adrenocorticotropic hormone (ACTH) by the pituitary. It is becoming increasingly evident that the pituitary secretes ACTH in response to influences reaching it from the central nervous system. Cortisol may suppress ACTH secretion by altering the rate at which corticotropin-releasing factors are elaborated by the central nervous system or by diminishing the responsiveness of the adenohypophysis to corticotropin-releasing factors. Whatever the mechanism, the higher the level of cortisol, the greater is the restraint on ACTH secretion. When supraphysiologic doses of cortisol are used in the treatment of inflammatory conditions, therefore, ACTH secretion is suppressed, and this leads to cessation of adrenocortical secretory activity, diminished responsiveness to exogenous ACTH, and progressive atrophy of the adrenal cortex. These changes in adrenocortical function are generally reversible if exogenous ACTH is administered or if cortisol administration is discontinued, permitting recovery of endogenous ACTH secretion.

Effects on protein metabolism. Cortisol apparently affects protein metabolism in a variety of ways. Which of the effects will ultimately come to be regarded as primary and which secondary cannot now be said. Cortisol-like steroids in supraphysiologic doses tend to accelerate the catabolism of protein. Cortisol increases the uptake of amino acids by the liver,[45] where deamination occurs which results in increased urea

production and gluconeogenesis. There is also acceleration of albumin synthesis by the liver, but the net rate of protein synthesis is usually less than that of protein and amino acid destruction.[55] In certain other tissues, cortisol interferes with the cellular uptake of amino acids; in this regard, cortisol appears to oppose the action of insulin. As a consequence of these catabolic and antianabolic actions, cortisol causes clinical manifestations of protein wasting. Children show growth retardation. Wasting of bone matrix results in osteoporosis. Wasting of the integument and increasing capillary fragility result in ecchymoses and cutaneous striae. Peptic ulcers may heal with difficulty. There may be poor wound healing.

Effects on carbohydrate metabolism. Cortisol not only stimulates gluconeogenesis from protein but also tends to oppose the action of insulin in transporting glucose across cell membranes.[44] Depending upon the dosage of cortisol and the compensatory capacity of the islets of Langerhans, varying degrees of impairment of glucose tolerance are seen. Latent diabetes may be converted to overt diabetes. With development of the diabetic state, there may be further acceleration of protein wasting.

Effects on adipose tissue. Cortisol in supraphysiologic doses promotes the deposition of adipose tissue in the facial, abdominal, and shoulder areas. It is not clear how, if at all, this might be related to the effects of cortisol in promoting ketone body formation by the liver and in promoting lipolysis in the epididymal fat pad of the rat.[32]

Effects on electrolyte metabolism. Cortisol promotes sodium retention and potassium excretion by stimulating cation exchange by the renal tubule. Opposing this effect is the tendency of cortisol to increase glomerular filtration rate, which in turn promotes sodium excretion. Usually, the effect on renal tubular ion exchange predominates, and the net result is sodium retention, occasionally to the point of edema formation. Rarely, however, the influence on glomerular filtration is greater, and diuresis of sodium may occur.[38] The increase in blood pressure which sometimes occurs during administration of cortisol is partially explained by the sodium-retaining action of this steroid; but, in addition, cortisol supports the blood pressure by increasing the responsiveness of blood vessels to norepinephrine. The potassium-wasting influence of cortisol may lead to hypokalemic-hypochloremic alkalosis.

Effects on lymphoid tissue and circulating eosinophils. Involution of lymphoid tissues and decreases in circulating lymphocytes are among the effects of large doses of cortisol. Antibody production tends to be suppressed. The eosinopenic action of cortisol is also well known, although its physiologic significance is obscure.

Search for a selectively anti-inflammatory steroid. Fundamental knowledge is too fragmentary at present to indicate whether the anti-inflammatory action of corticosteroids is necessarily dependent upon some metabolic process which would inevitably associate it with undesirable side effects. All of the currently available anti-inflammatory steroids affect "organic" metabolism in such a manner as to cause protein (nitrogen)–wasting, hyperglycemia, eosinopenia, ACTH suppression, etc. For several years, there has been an active search for a selectively anti-inflammatory steroid. For want of fundamental information, however, the approach to the development of such an agent has remained entirely empirical.

Problems of assay

It is still necessary to assay the metabolic and anti-inflammatory properties of a new steroid in human subjects before one can conclude with certainty whether the compound in question has a therapeutic advantage over older agents. A large number of useful methods of assaying various steroidal properties have been developed in rats, but such assays are of limited value in predicting clinical properties of steroids. Species differences are sometimes observed

with respect to responses to steroids. For example, a number of steroids which cause acute increases in sodium excretion in the rat have been found to be potent sodium-retaining agents when administered to man. Some compounds which are extremely effective anti-inflammatory agents in the rat as measured by granuloma inhibition have been disappointing in the therapy of inflammatory disorders in man. Occasionally, assays in rats do not agree with those in human subjects because different routes of administration of steroids have been employed for the two assays. Various preparations differ greatly in their ability to escape metabolic inactivation when absorbed via the portal circulation. A compound which is very effective when administered intramuscularly may be quite ineffective when given orally. Furthermore, a steroid which is readily absorbed from the gastrointestinal tract may be so slowly absorbed from an intramuscular injection site that it appears to be inactive by this route. For example, hydrocortisone acetate is so slowly absorbed from an intramuscular injection site that it has little or no biologic activity over a period of several days after a single injection, but when administered orally, it is quickly effective and almost as potent as intravenous cortisol. In contrast, aldosterone is maximally effective when administered intramuscularly but almost totally ineffective when administered orally, presumably because it is rapidly inactivated by the liver after absorption from the gastrointestinal tract.[17] Since most of the corticosteroid derivatives which are employed for anti-inflammatory purposes in clinical medicine are preferably administered orally, it would seem advantageous to carry out preliminary assays in rats by this route.

Although steroids which are proposed for clinical use must ultimately be assayed in human subjects, it is by no means an easy matter to obtain valid quantitative data in man. One of the major problems in assaying steroids in human subjects is that of eliminating subjectivity on the part of both the patient and the physician. A well-designed double blind study, employing two or more active compounds identifiable only by code number, is unfortunately rare in the clinical evaluation of steroids. Therapeutic responses and side effects are usually difficult to quantitate. Sometimes they are nothing more than clinical impressions. Most clinical reports that give estimates of potency of steroids make no effort to appraise the confidence limits of such estimates.

Another major problem encountered in the metabolic evaluation of steroids is related to the metabolic lability of sick patients. A patient with fever, variable food intake, labile diabetes, severe hyperthyroidism, or diarrhea, for example, can hardly be the subject of a worthwhile study of the effect of a steroid on nitrogen balance. It is not easy to study the catabolic potency of steroids even in the metabolically stable patient. Although it is common knowledge that the anti-inflammatory steroids cause nitrogen wasting, there are in the medical literature no statistically reputable assays of the nitrogen-wasting effects of corticosteroids in man. There have been no studies in which two or more steroids were given in graded dosages to comparable series of subjects while nitrogen balance was quantitated in such a way that a ratio of potency (with confidence limits) could be calculated for the two steroids.

It has been possible, nevertheless, to assay in man some of the properties of corticosteroids in quantitative fashion. A major consideration in the design of such assays has been the requirement that adventitious fluctuations in the crucial parameter be reduced to a minimum. In this laboratory, the ACTH-suppressing activity of corticosteroids has been assayed in nonstressed individuals by observing the percentage decrease in endogenous urinary corticosteroids during a 2-day course of treatment. The eosinopenic activity of corticosteroids has been assayed in nonstressed individuals by observing the percentage decrease in

circulating eosinophils at intervals of 4 and 7 hours after administration of a single dose of the agent. Hyperglycemic activity has been assayed by determining the blood glucose level 1 hour after a rapid intravenous injection of glucose, the steroid having been administered 8 hours earlier.[59] Anti-inflammatory activity has been evaluated by determining through trial and error what doses of an "unknown" compound can be used interchangeably with a "standard" steroid with equivalent therapeutic effects in patients with rheumatoid arthritis.[10] A few attempts have been made to assay nitrogen-wasting activity of corticosteroids by observing the increase in urinary nitrogen during administration of graded doses of the agents to metabolically stable subjects receiving constant diets. Sodium-retaining and potassium-wasting activities have been evaluated in similar fashion.

Structure-function relationships of corticosteroids

The ingenuity of steroid chemists has provided several hundred synthetic corticosteroid derivatives for biologic evaluation during the past 8 years. All of the steroids which have been shown to have anti-inflammatory activity in man have had the basic structure Δ^4-pregnene-11β-ol-3, 20-dione and two or more potentiating substituents (Fig. 1). Anti-inflammatory activity is enhanced by the presence of the following structural components: Δ^1, 9α-halogen, 16-methyl, 17α-hydroxyl, and 21-hydroxyl. It is attenuated by the presence of Δ^6, 14α-hydroxyl, and 16α-hydroxyl components.

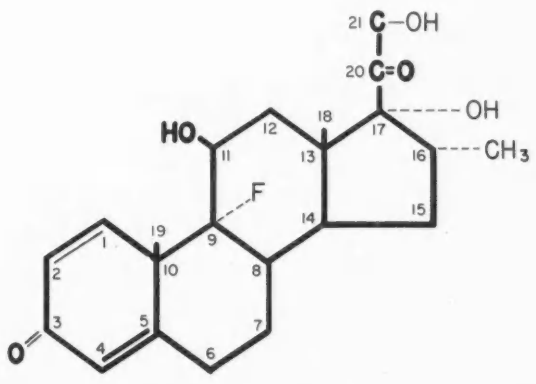

Fig. 1. The bold lines and letters indicate the structure of Δ^4-pregene-11β-ol-3, 20-dione, which is common to all steroids that have been shown to have anti-inflammatory activity in man. Substituents which individually are nonessential but which, if present, enhance anti-inflammatory potency are represented by light lines and letters.

All corticosteroids which have been shown to possess significant electrolyte-regulating activity have had the basic structure Δ^4-pregnene-3,20-dione and one or more potentiating substituents. Mineralocorticoid activity is enhanced by the presence of the following structural components: 2α-methyl (if 11β-hydroxyl is present), 9α-halogen, and 21-hydroxyl. It is attenuated by the presence of 16α-hydroxyl, 16-methyl, and 17α-hydroxyl substituents.

Single modification. Apparently minor changes in chemical structure of a steroid may greatly alter its biologic activity. The importance of various steroid components can be illustrated by comparing the biologic activity of cortisol with various analogues each of which differs in only one structural feature from cortisol itself.

17-Desoxycortisol (corticosterone). The 17-hydroxyl group selectively enhances the potency of a steroid as a regulator of organic metabolism without enhancing its electrolyte regulating potency; 17-desoxycortisol has negligible anti-inflammatory activity in man although it possesses electrolyte-regulating activity at least equivalent to that of cortisol.[16]

21-Desoxycortisol. That the 21-hydroxyl group is an important determinant of corticosteroid potency is indicated by the fact that 21-desoxycortisol has very little biologic activity of any sort.[28, 48]

11β-Hydroxyl group. The crucial importance of the 11β-hydroxyl group is illustrated by comparing cortisol with the following three steroids: 11-epicortisol, cortisone, and 11-desoxycortisol. The 11α-hydroxy epimer of cortisol is devoid of biologic activity.[46] Cortisone, which differs structurally from cortisol only by substitu-

tion of an 11-keto for an 11β-hydroxyl group, has approximately 70 per cent of the biologic potency of cortisol.[8] Normally, in the body, there is enzymatically facilitated interconversion between the 11-keto and the 11β-hydroxy forms of corticosteroids which results in the net conversion of about 70 per cent of administered cortisone to cortisol.[47] The percentile agreement in these observations supports the concept that the biologic activity of cortisone is contingent upon its conversion to cortisol. Further evidence that this is the case is afforded by the demonstration that when interconversion of 11-keto and 11β-hydroxyl groups is blocked by the presence of some structure such as a 2α-methyl group, the 11β-hydroxy form of the steroid is fully active while the 11-keto is biologically inert.[15] When injected intra-articularly, cortisone has been found to be far less effective than cortisol, presumably because the synovium lacks the capacity to convert cortisone to cortisol.[47] 11-Desoxycortisol (Reichstein's substance S) is devoid of anti-inflammatory activity in man.[48] In doses up to 400 mg. per day, it does not affect nitrogen balance, eosinophil levels, or glucose tolerance but does have some electrolyte-regulating activity.

Δ¹-Cortisol. 1, 2-Dehydrocortisol (prednisolone) is approximately four times as potent an anti-inflammatory agent as cortisol,[12] but the electrolyte-regulating activity of cortisol is not enhanced by 1, 2-dehydrogenation. Relative freedom from electrolyte effect has been responsible for very wide acceptance of this agent by clinicians. 1, 2-Dehydrogenation has been found to enhance the potency of all anti-inflammatory steroids thus far tested. Some of these are listed in Table I. A partial explanation for the greater potency of Δ¹ steroids is found in the observation that they are metabolized more slowly than their 1, 2-saturated analogues. In man, the halftime of circulating cortisol is about 120 minutes while that of Δ¹-cortisol is about 200 minutes.[13] This explanation fails to account for the qualitative difference between cortisol and Δ¹-cortisol, that is, the *selective* increase in organic activity without any increase in electrolyte-regulating activity in the case of the Δ¹ derivative.

2α-Methylcortisol. This compound is approximately equal to cortisol in causing eosinopenia, nitrogen-wasting, and suppression of ACTH. It is, however, approximately 25 to 50 times as potent as cortisol in promoting sodium retention and potassium excretion.[36] The great potency of this compound as an electrolyte regulator has precluded its use as an anti-inflammatory agent. Introduction of a methyl group in 2α position has been shown to enhance the electrolyte-regulating potency of a large number of 11β-hydroxycorticosteroids (Table II). On the other hand, introduction of a methyl group in 2α position has resulted in loss of biologic activity of 11-desoxy or 11-keto compounds. For example, 2α-methyl-11-desoxycorticosterone has only about 0.08 times the electrolyte-regulating potency of 11-desoxycorticosterone.

6α-Methylcortisol. This agent is slightly more effective than cortisol in assays of anti-inflammatory, eosinopenic, nitrogen-wasting, and electrolyte-regulating activities in man. It is impossible to generalize concerning the biologic consequences of 6α-methylation. Of the various compounds modified in this way, some show increased and others decreased potency when compared with their nonmethylated analogues.[37]

9α-Fluorocortisol. Fludrocortisone is more potent than cortisol with respect to all biologic activities.[26] Its anti-inflammatory, eosinopenic, ACTH-suppressing, hyperglycemic, and nitrogen-wasting activities exceed those of cortisol by an eightfold to tenfold factor.[9, 37] In acute assays of electrolyte-regulating activity in both dogs and man, 9α-fluorocortisol is about 125 times as potent as cortisol. This effect has precluded the therapeutic use of 9α-fluorocortisol for any condition other than adrenal insufficiency. As shown in Table III, the introduction of a 9α-halogen substituent increases the biologic activity of

Table I. *Effect of 1,2-dehydrogenation upon biologic activities of corticosteroids*

Compound	Organic potency		Electrolyte-regulating potency	
	1, 2-Saturated steroid	*Δ^1 Analogue*	*1, 2-Saturated steroid*	*Δ^1 Analogue*
Cortisol	1	4[12]	1	0.8[37]
6-αMethylcortisol	1.3[37]	5[37]	2[37]	0.5[37]
9α-Fluorocortisol	10[9]	20[5]	125[36]	200[38]
6α-Methyl-9α-fluorocortisol	8[37]	22[37]	110[37]	58[37]
16α-Hydroxycortisol	< 1[4]	1.5[4]	Nil[4]	Nil[4]
16α-Methylcortisol	2*	5[11]	Nil*	Nil*

*G. W. Liddle and M. Fox: Unpublished data.

Table II. *Effect of 2α-methylation upon the biologic activities of corticosteroids*

Compound	Organic potency		Electrolyte-regulating potency	
	Nonmethylated steroid	*2-Methyl analogue*	*Nonmethylated steroid*	*2-Methyl analogue*
Cortisol	1	0.7[36]	1	25[36]
Δ^1-Cortisol	4[12]		0.8[37]	240[23]
9α-Fluorocortisol	10[9]	5[36]	125[36]	2,500[36]
11β-Hydroxyprogesterone			0.4[36]	1.7[36]
Cortisone	0.7[47]	0.4[22]	0.7[47]	0.2[36]
11-Desoxycorticosterone	Nil[57]		25[36]	1.5[36]

Table III. *Effect of 9α-fluorination upon biologic activities of corticosteroids*

Compound	Organic potency		Electrolyte-regulating potency	
	Nonfluorinated steroid	*9α-Fluoro analogue*	*Nonfluorinated steroid*	*9α-Fluoro analogue*
Cortisol	1	10[9]	1	125[36]
Δ^1-Cortisol	4[12]	20[5]	0.8[37]	200[38]
2-Methylcortisol	0.7[36]	5[36]	25[36]	2,500[36]
6α-Methylcortisol	1.3[37]	8[37]	2[37]	110[37]
Δ^1-16α-Hydroxycortisol	1.5[4]	5[6]	Nil[4]	4*[38]
Δ^1-16α-Methylcortisol	5[11]	30[11]	Nil[11]	12†

*Potassium loss only.

†G. W. Liddle and M. Fox: Unpublished data.

Table IV. *Effects of 16α-hydroxylation upon biologic activities of corticosteroids*

Compound	Organic potency		Electrolyte-regulating potency	
	16-Desoxy steroid	*16α-Hydroxy analogue*	*16-Desoxy steroid*	*16α-Hydroxy analogue*
Cortisol	1	<1[4]	1	Nil[4]
Δ^1-Cortisol	4[4]	1.5[4]	Nil[4]	Nil[4]
2α-Methyl-9α-fluorocortisol	5[36]	2[4]	2,500[36]	<25[4]
Δ^1-9α-Fluorocortisol	20[5]	5[6]	200[38]	4*[38]
11-Desoxycorticosterone	Nil[57]		25[36]	0[2]

*Potassium loss only.

Table V. *Effects of 16α-methylation upon biologic activity of corticosteroids*

Compound	Organic potency		Electrolyte-regulating potency	
	Nonmethylated steroid	*16α-Methyl analogue*	*Nonmethylated steroid*	*16α-Methyl analogue*
Cortisol	1	2*	1	Nil*
Δ¹-Cortisol	4[12]	5[11]	0.8[37]	Nil*
9α-Fluorocortisol	10[9]	12[11]	125[36]	Nil[11]
Δ¹-9α-Fluorocortisol	20[5]	30[11]	200[38]	12[38]
Δ¹-9α-Fluoro-21-desoxy-cortisol	0.1[37]	5*	12[37]	Nil*

*G. W. Liddle and M. Fox: Unpublished data.

any corticosteroid. Since electrolyte-regulating activity is enhanced out of proportion to organic activity, only those 9α-halogenated corticosteroids which have an additional modification which nullifies electrolyte-regulating activity have been considered suitable for clinical use as anti-inflammatory agents.

16α-Hydroxycortisol. This compound is less effective than cortisol in regulating organic metabolism; it is entirely devoid of sodium-retaining activity. A number of 16α-hydroxycorticosteroids have been investigated (Table IV). In every case, the introduction of a hydroxyl group in the 16α position has resulted in some diminution of organic activity and marked attenuation of electrolyte regulating activity.

16α-Methylcortisol. This agent, developed by Arth and associates,[1] is approximately twice as potent as cortisol in regulation of organic metabolism in man. It is virtually lacking in sodium-retaining activity. The relative potencies of a series of steroids and their 16α-methylated analogues are listed in Table V. In every case, the 16α-methylated derivative has been found to be slightly more potent than its nonmethylated analogue in organic activity but far less effective in electrolyte regulation. Although the orientation of substituent groups in relation to the plane of the steroid nucleus is generally of crucial importance in determining the biologic activity of the compound, in the case of 16-methylation it makes little difference whether the methyl group is located in the α or β position.

Effects of multiple modification. The introduction of two or more modifications into the structure of a corticosteroid frequently results in alterations in biologic activity which are multiplicative.[27] It is sometimes of interest to attempt to predict the potency of a synthetic steroid by multiplying the effects of individual substituents. In Tables VI and VII, the potency factors for individual substituents are listed. In addition, the "predicted" potency and "empirical" potency of some multimodified cortisol derivatives are presented. Three multimodified steroids which are in general use as therapeutic agents merit special mention.

Methylprednisolone. Δ¹-6α-Methylcortisol is the most widely used of the 6α-methyl corticosteroid derivatives. In man, methylprednisolone is about 5 times as potent as cortisol with respect to anti-inflammatory, ACTH-suppressing, nitrogen-wasting, and eosinopenic activities.[10] It has minimal sodium-retaining potency. The difference be-

Table VI. *Potency factors for substituent groups*

Group	*Anti-inflammatory activity*	*Electrolyte-regulating activity*
Δ¹	4	0.8
2α-Methyl	0.7	25
9α-Fluoro	10	125
16α-Hydroxyl	0.5	0.005
16α-Methyl	2	<1
6α-Methyl	1.3 (variable)	2 (variable)

tween this compound and cortisol is largely attributable to the Δ^1 modification. 6α-Methylprednisolone is only slightly more effective than Δ^1-cortisol (prednisolone) in regulating organic metabolism and only slightly less active in its effects upon electrolyte metabolism.

Triamcinolone. Δ^1-9α-Fluoro-16α-hydroxycortisol is about 4 to 5 times as potent as cortisol with respect to anti-inflammatory, ACTH-suppressing, nitrogen-wasting, and eosinopenic activities. Triamcinolone is devoid of sodium-retaining activity but does cause some potassium loss. The enhanced organic activity of triamcinolone is due entirely to the Δ^1 and 9α-fluoro modifications. Δ^1-9α-Fluorocortisol is 20 to 25 times as potent as cortisol itself in regulating organic metabolism, whereas triamcinolone is only 4 to 5 times as potent as cortisol. On the other hand, freedom from sodium-retaining activity is due entirely to the 16α-hydroxy substituent. Δ^1-9α-Fluorocortisol is about 200 times as potent as cortisol in promoting sodium retention, whereas triamcinolone has no sodium-retaining activity.

Dexamethasone. Δ^1-9α-Fluoro-16α-methylcortisol is about 30 times as potent as cortisol with respect to ACTH-suppressing, eosinopenic, hyperglycemic, and anti-inflammatory activities.[11] In dosages of less than 6 mg. per day, this steroid causes virtually no sodium retention. With higher dosages, however, significant sodium retention may occur. The very great organic potency of dexamethasone is a function of all three synthetic substituents (Δ^1, 9α-fluoro, and 16α-methyl). The relative freedom from electrolyte-regulating activity is attributable to the 16α-methyl group, inasmuch as the nonmethylated analogue (Δ^1-9α-fluorocortisol) is a very potent sodium-retaining agent.

Dissociation of glucocorticoid functions. All of the steroids which are in general use as anti-inflammatory agents have prominent protein-wasting, hyperglycemic, ACTH-suppressing, and eosinopenic activities. Usually a modification of structure which alters one of these biologic activities also brings about commensurate alterations with respect to the others. Occasionally, partial dissociation of some of these activities has been observed in animal assays, but usually these observations have not been confirmed when the same steroids were assayed in man.

It has recently been possible, however, to demonstrate significant degrees of dissociation of these various properties when certain steroids were administered to human subjects.[33] All of the steroids exhibiting dissociation of various "organic" activities lacked 21-hydroxyl groups. All of them were less potent than their 21-hydroxylated analogues with respect to all biologic activities. ACTH-suppressing activity was only moderately diminished, but eosinopenic and hyperglycemic activities were greatly attenuated. For example, Δ^1-9α-fluoro-21-desoxycortisol was approximately 2 times as potent as cortisol in assays of ACTH suppression but only 0.2 and 0.1 times as potent in assays of hyperglycemic and eosinopenic activities, respectively.

Table VII. *Predicted and empirical potencies of multimodified cortisol derivatives*

Compound	*Anti-inflammatory potency relative to cortisol*		*Electrolyte-regulating potency relative to cortisol*	
	Predicted	*Empirical*	*Predicted*	*Empirical*
Δ^1-9α-Fluorocortisol	40	20	100	200
2α-Methyl-9α-fluorocortisol	7	5	3,125	2,500
Δ^1-9α-Fluoro-16α-hydroxycortisol	20	5	0.5	4*
Δ^1-9α-Fluoro-16α-methylcortisol	80	30	<100	@12
Δ^1-6α-Methylcortisol	5	5	1.6	0.5

*Potassium loss only.

Unfortunately, the agents which have been shown to have dissociated activities are not particularly promising as anti-inflammatory agents. Demonstration that various properties of corticosteroids can be separated is of theoretical importance, however, and strengthens the hope that therapeutic agents of increasingly specific action might yet be developed.

Some pharmacologic considerations

Seven steroids are available for clinical use as systemic anti-inflammatory agents: cortisone acetate, hydrocortisone (cortisol), prednisone,* prednisolone, methylprednisolone, dexamethasone, and triamcinolone. All of these agents are effective when administered orally. They are rapidly absorbed and disappear from the circulation with a halftime of 1 to 3 hours. Differences in potency are not adequately explained by differences in rates of metabolism. Maximum biologic effect is seen from the second to eighth hour after administration of a given dose, lagging considerably behind the maximal blood level of the steroid. In order to achieve maximal effect "around the clock," it is necessary to give these steroids in repeated doses. A metabolic rebound begins within several hours after the last dose is administered; exacerbation of inflammatory symptoms does not usually become severe until about 24 hours after administration of the last dose.

If appropriate adjustment in dosage is made, any of these compounds may be used interchangeably in bringing about anti-inflammatory effects. The relative potencies of these compounds when used for anti-inflammatory purposes are as follows: hydrocortisone 1, cortisone 0.7, prednisone 4, prednisolone 4, triamcinolone 5, methylprednisolone 5, and dexamethasone 30. They all share the desirable effects of hydrocortisone; and, except for electrolyte-regulating activity, they all share the undesirable effects of hydrocortisone. Cortisone and hydrocortisone have enough electrolyte-regulating activity to be troublesome when used in dosage greater than 75 mg. per day. At usual dosage levels, dexamethasone, prednisone, prednisolone, and methylprednisolone are practically free of electrolyte-regulating activity. Only triamcinolone is completely free of sodium-retaining activity. Triamcinolone also has certain other properties which seem to set it off as qualitatively different from the other corticosteroids. When used in very large doses, it is reputed to be especially apt to cause mental depression, anorexia, and muscle wasting. It is also said to be of unique value in the treatment of psoriasis.

The following water-soluble steroid esters are available for injection in convenient concentrations: hydrocortisone hemisuccinate (50 mg. per milliliter), hydrocortisone phosphate (50 mg. per milliliter), and dexamethasone phosphate (4 mg. per milliliter). These esters may be given intravenously, but after intramuscular or subcutaneous administration, they also reach the blood stream in effective concentration almost immediately. Maximal concentration is attained within several minutes, after which the steroid disappears from the circulation with a halftime of about 2 hours. These soluble esters are ideal for emergency treatment.

Hydrocortisone (free alcohol), cortisone acetate, and methylprednisolone acetate are available for intramuscular injection in aqueous suspension. Hydrocortisone administered in this manner is absorbed over a period of 4 to 8 hours, cortisone acetate is more slowly absorbed over a period of 24 to 48 hours, and methylprednisolone acetate is even more slowly absorbed over a period of about 5 days. One should not make the mistake of giving hydrocortisone *acetate* suspension intramuscularly in place of hydrocortisone; the acetate is extremely slowly absorbed from an intramuscular injection site over a period of several weeks. Small quantities of hydrocortisone acetate, prednisolone trimethylacetate, and methyl-

*Prednisone is the official pharmaceutical name for Δ^1-cortisone.

prednisolone acetate may be given intra-articularly. Even though the steroid disappears from the synovial fluid within approximately 2 hours, an anti-inflammatory response in the injected joint persists for 1 to 2 weeks after the injection. Cortisone acetate and prednisone acetate are said to be ineffective when administered by the intra-articular route, presumably because synovial tissues are incapable of converting these 11-ketosteroids to their active 11β-hydroxy analogues.

Hydrocortisone, hydrocortisone acetate, methylprednisolone, 9α-fluorohydrocortisone, and dexamethasone are all available in the form of ointments for topical application to the skin. Corticosteroids are absorbed in negligible quantities through intact skin. Appreciable quantities may be absorbed if applied to extensive areas of denuded skin, but untoward effects from systemic absorption of topical steroids are almost never encountered. Two additional agents are useful topically: triamcinolone acetonide and fluorometholone (Δ^1-6-methyl-9α-fluoro-21-desoxycortisol). These two agents are peculiar in exhibiting much higher ratios of potency (relative to cortisol) when administered topically than when administered systemically.

Therapeutic uses of corticosteroids as anti-inflammatory agents

General. It has already been mentioned that the use of corticosteroids in anti-inflammatory dosage carries with it certain untoward metabolic effects which are recognizable clinically as Cushing's syndrome medicamentosus. It should be remembered, however, that the untoward metabolic effects of corticosteroids are those of prolonged usage. There is no contraindication to a single dose of corticosteroid. In general, the shorter the course of corticosteroid therapy, the less likely one is to encounter any undesirable effects whatever. In making the decision to employ anti-inflammatory steroids for more than a few days, the physician must consider whether the disease which he is attempting to suppress is more dangerous to the patient than the Cushing's syndrome which he might induce. Corticosteroid therapy should be regarded as a measure to supplement rather than to supplant other standard aspects of therapeutic management. Corticosteroids should be used in whatever dosage is necessary and without hesitation when such therapy can be expected to save a life or prevent serious incapacitation. Even when a disease is not life threatening, Cushing's syndrome medicamentosus might on occasion be considered a justifiable price to pay in order to avoid the incapacitation of an inflammatory disorder, particularly if the patient is the head of a family.

Rheumatoid arthritis. The original and still the most common condition for which anti-inflammatory steroids are employed is rheumatoid arthritis. Opinions vary widely as to the proper place of steroids in the management of patients with this disease. It is my view that since the condition is not life threatening, one should not employ steroids until it is apparent that all other reasonable measures will fail to restore the patient to a productive life. A regimen of rest, physiotherapy, salicylates, and perhaps other measures should first be employed.[25] If after a reasonable period the patient is unable to return to a productive existence, steroid therapy may be *added* to this regimen. Generally, economic pressures are powerful factors in determining what is a reasonable trial of nonsteroid therapy. When steroids are used for this condition, it should be recognized that the patient will probably not be readily withdrawn from steroid therapy. Dosage should be kept at a minimum consistent with achieving the therapeutic objective of having the patient return to a productive life. If his work requires too much use of diseased joints, an effort should be made to change his activities. Most patients will obtain substantial benefit from the equivalent of 10 mg. of prednisone daily. This dose is generally attended by only mild manifestations of Cushing's syndrome. The

majority of patients treated in this fashion can be expected to maintain substantial improvement for 5 years or longer. There is no convincing evidence that the patient's chance for a spontaneous remission will be materially altered by steroid therapy. Destructive joint changes can progress during steroid therapy. On the other hand, some patients without steroid therapy allow their painful joints to become immobilized and ankylosed to the point of complete loss of function. Steroids, if started early enough, would probably prevent this.

A fair degree of success has been achieved in treatment of individual joints with intra-articular hydrocortisone acetate. Such treatment is useful not only in selected cases of rheumatoid arthritis but in patients with osteoarthritis of the knee. With such therapy, the undesirable effects of systemic hypercortisolism are avoided. There are the slight risks, however, of inducing an aseptic flare of symptoms for 1 to 2 days after the injection or of introducing staphylococcal infection into the joint.

Rheumatic fever. There is general agreement that in acute rheumatic fever with carditis, pericardial effusion, and congestive heart failure, corticosteroids in large doses may be lifesaving. There is no good evidence, however, that steroids as ordinarily used will modify the incidence of chronic valvulitis. The other manifestations of acute rheumatic fever are self-limited, generally respond well to salicylates and bed rest, and do not call for steroid therapy. In managing the carditis of acute rheumatic fever, one should be prepared to give whatever dose of steroid is necessary. Usually a prompt response is observed with the equivalent of 60 mg. of prednisone per day. After satisfactory improvement has been achieved, the steroid may be gradually withdrawn over a period of 10 days or more.

Disseminated lupus erythematosus. There is probably no other situation in which so much flexibility is required in adapting corticosteroid dosage to the needs of the patient as in disseminated lupus erythematosus. The diagnosis of this condition does not automatically make patients candidates for steroid therapy, but sooner or later approximately two-thirds of them will require steroids. If manifestations are mild and not life threatening, it is advisable to temporize with the use of salicylates and antimalarial drugs, but one should not hesitate to use steroids in the patient with disseminated lupus erythematosus who exhibits frank hemolytic anemia or evidence of renal or neurologic involvement. In treating any of these complications, the proper dose of steroid is whatever amount is necessary to control the condition. The equivalent of 100 mg. of prednisone per day may frequently be necessary to control hemolysis, nephropathy, or encephalopathy.

Lupus nephritis is not amenable to steroid therapy unless treatment is initiated before the blood urea nitrogen level becomes significantly elevated. Results of treatment of lupus nephritis have not been good when small doses of steroids were employed. After the manifestations of nephropathy have disappeared under the influence of large doses of corticosteroids, it is probably advisable to treat with doses of the order of 40 to 60 mg. of prednisone per day for as long as 6 months before adjusting to ordinary maintenance dosage.

In treating nonrenal complications of lupus, steroid dosage may be reduced somewhat earlier if the clinical condition permits.

Approximately 10 per cent of patients with disseminated lupus erythematosus will at some time experience a crisis, an acute fulminant exacerbation of symptoms including fever and psychosis or convulsions. This frequently lethal complication constitutes a clear-cut indication for corticosteroids in massive dosage.[30] The equivalent of 100 to 500 mg. of prednisone per day should be employed until the crisis is over. Dosage should be tapered gradually and should be raised again promptly if the manifestations of crisis reappear.

After a period of several weeks, these patients may do well on ordinary doses of corticosteroids or even tolerate the complete withdrawal of corticosteroids without recurrence of severe symptoms.

In the management of patients with disseminated lupus erythematosus who are not in crisis and who do not have hemolytic anemia, thrombocytopenia, active renal disease, or neurologic complications, the principles of therapy are similar to those described for treatment of rheumatoid arthritis.

Thrombotic thrombocytopenic purpura. This rapidly fatal condition is usually unresponsive to small doses of corticosteroids, but the prompt use of large amounts of corticosteroids (100 mg. of prednisone daily for at least several weeks) has been accompanied by remission of symptoms with ultimate recovery which has been maintained after complete withdrawal of steroid therapy.[14] Further experience is needed to determine the ultimate value of prompt, vigorous corticosteroid therapy in this otherwise fatal disorder.

Idiopathic thrombocytopenic purpura. This potentially fatal condition often responds favorably to corticosteroid therapy.[18, 42] Although the blood platelet concentration may remain low, the use of moderate amounts of corticosteroids (equivalent to 10 to 50 mg. of prednisone daily) usually controls clinical purpura and normalizes the bleeding time and capillary fragility.[29, 54] Massive corticosteroid therapy (200 to 300 mg. of prednisone daily) will frequently elevate the platelet count and may occasionally be required to control bleeding.[58] A high percentage of children with idiopathic thrombocytopenic purpura will in time experience lasting remissions; it is fully justifiable, therefore, to suppress the bleeding tendency by means of corticosteroids for 3 or 4 months or even longer with the expectation that spontaneous recovery will occur. In adults, on the other hand, permanent remissions occur in a comparatively small percentage, and it is scarcely justifiable in most cases to depend upon corticosteroid therapy for longer than 2 or 3 months before resorting to splenectomy as the definitive form of treatment.[20]

Autoimmune hemolytic anemia. This is another potentially fatal disorder which can often be controlled by means of corticosteroid therapy. Large doses may be necessary to control hemolysis. Corticosteroids may be particularly valuable in preventing rapid hemolysis of transfused blood. Continued employment of large doses of corticosteroids may be necessary for a matter of months. As the hematologic disorder permits, however, dosage should be reduced. In some cases, the basic disorder will undergo remission, permitting complete withdrawal of steroid therapy. In other cases, corticosteroids must be continued indefinitely; usually, doses of prednisone in the range of 5 to 15 mg. per day will suffice. If larger doses are required for more than 6 months, splenectomy should be considered.

Nephrosis associated with membranous glomerulonephritis. Among adults, particularly in Negroes, this condition progresses to fatal glomerulonephritis in a large majority of cases within 2 to 4 years. The outlook is on the whole somewhat less grim in children, but the following generalizations are still applicable. Small doses of corticosteroids are not effective in altering the ultimate course of the disease. Prognosis is significantly improved, however, by use of large doses of steroids, provided vigorous therapy is begun early.

A suitable regimen might include the equivalent of 40 to 120 mg. of prednisone per day until the urine is protein free; this usually occurs within 10 to 14 days. Steroid dosage is then dropped to a level of 30 to 40 mg. of prednisone daily for 3 to 6 months. It is advisable to continue treatment for an additional year with steroid dosage equivalent to 30 mg. of prednisone daily for 3 days each week, allowing 4 days for metabolic restoration.[34, 41, 50] A daily check for proteinuria should be made, and its recurrence at any time calls for an

immediate increase in corticosteroid therapy until complete control of the activity of the renal lesion is once again achieved. Ultimately, corticosteroid therapy can be completely withdrawn, but even in the remote follow-up period, these patients should be expected to develop recurrence of proteinuria whenever they suffer an "antigenic challenge." If this occurs, another course of corticosteroid therapy is in order.

Steroid therapy has not been of value in nephrosis associated with amyloidosis or diabetic glomerulosclerosis.

Dermatomyositis. Corticosteroids are of definite value in treating dermatomyositis. The proper dosage is whatever is necessary to produce a remission. This is usually in the range of 20 to 80 mg. of prednisone per day. As improvement occurs, dosage should be gradually tapered. It is frequently possible to withdraw steroid therapy altogether or to reduce dosage to levels producing only very minor untoward effects. Anabolic steroids are often recommended for use in combination with corticosteroids in order to minimize the severe muscle wasting which characterizes this disease.

Uveitis. Ophthalmic solutions of hydrocortisone or its derivatives may be very useful in the treatment of granulomatous anterior uveitis. By this means, high concentrations of steroid can be attained in the area of inflammation without producing the high systemic levels which give rise to the major side effects of steroid therapy. If uveitis is incompletely controlled by topical steroids, one should not hesitate to use systemic steroids in liberal dosage. Such therapy may be necessary to prevent loss of vision. Control of the process can be achieved generally within a few weeks, and steroid therapy may then be gradually withdrawn.

Pemphigus. This lethal condition can be controlled with corticosteroids, although massive dosage is often required. As the skin lesions heal, steroid therapy should be gradually reduced to the lowest level that will prevent the appearance of new lesions. It is rarely possible to withdraw therapy completely for any extended period of time.

Exfoliative dermatitis. Corticosteroids in high dosage for limited periods of time may be of great value in controlling the distressing manifestations of generalized exfoliative dermatitis. Every effort should be made to determine and eliminate primary etiologic factors. Other, nonsteroidal measures are also extremely valuable, especially in the treatment of the secondary infection which commonly accompanies exfoliative dermatitis.

Generalized eczema. Since this is a chronic, nonfatal disorder, corticosteroid therapy should not be employed except in controlling severe acute exacerbations. Large doses may be required to achieve satisfactory control of symptoms; while such large doses might be justifiable over short periods, they would be unjustifiably hazardous if used chronically. Withdrawal of steroid therapy is sometimes associated with severe exfoliative dermatitis. Possible etiologic factors should be sought, and all reasonable nonsteroidal measures should be employed.

Localized atopic dermatitis (eczema). Topical application of corticosteroids may be employed with gratifying results in localized allergic dermatoses. Allergenic factors should be eliminated whenever possible. There are no serious untoward effects of topical steroid therapy over limited areas. Because of the expense of proprietary ointments, many dermatologists compound their own topical steroid preparations.

Acute allergic reactions: Angioneurotic edema, serum sickness, and trichinosis. In these distressing but usually self-limited conditions, corticosteroids in large doses may be used with dramatic effect. Treatment can be limited to a period of hours or days.[40, 51]

Allergic rhinitis. Corticosteroids may be employed in addition to conventional measures in managing severe acute ex-

acerbations of allergic rhinitis. They have no place in the chronic management of this benign condition.

Bronchial asthma. This allergic disorder can generally be managed best by the use of bronchodilators, protection of the patient from allergens, etc. Steroid therapy should never be used as a substitute for conventional measures. Frequently, however, conventional measures prove to be inadequate, and there may be severe acute exacerbations which require short-term use of steroids in doses equivalent to 20 to 100 mg. of prednisone per day. Steroids may be lifesaving in treatment of status asthmaticus. Such high dosage can usually be withdrawn within a few days, and steroids should be completely withdrawn from the regimen whenever possible. Patients with prolonged intractable asthma who are distressed or incapacitated despite the employment of all conventional measures can justifiably be placed on chronic steroid therapy. Dosage of the order of 10 mg. of prednisone daily may restore these patients to comfortable productive lives without entailing prohibitive effects. This should be done, however, with full realization of the metabolic complications which may ensue and cognizance of the physical and psychologic dependence which will make steroid withdrawal difficult, if not impossible.

Sarcoidosis. Hypercalcemia of sarcoidosis presents an urgent indication for steroid therapy in order to forestall the development of nephrocalcinosis and renal lithiasis. The equivalent of 20 to 30 mg. of prednisone per day usually controls the hypercalcemia within 2 to 4 days.[31] Careful long-term follow-up is in order, and corticosteroid therapy should be employed whenever hypercalcemia recurs. In some patients, a useful long-term regimen is that of prednisone 20 to 30 mg. per day for 3 days of each week. This regimen is not associated with untoward metabolic effects. Other measures such as high water intake, low calcium diet, and avoidance of vitamin D are also recommended.

Serious irreversible pulmonary insufficiency may occur if sarcoid infiltration of the lung is allowed to progress too far.[56] Early treatment as outlined for the treatment of hypercalcemic sarcoidosis should be instituted.

Central nervous system sarcoidosis with hypothalamic-pituitary dysfunction[52] or with interruption of spinal cord pathways[43] may respond well to corticosteroid therapy. A course of treatment with dosage in the range of 15 to 30 mg. of prednisone a day until the principal manifestations clear is recommended. If there is any tendency for the lesion to recur, long-term intermittent therapy may be advisable.

Intermittent steroid therapy has not received extensive trial in the management of sarcoidosis, and these recommendations may require modification as additional experience is acquired.

Nontropical sprue. Intestinal malabsorption due to nontropical sprue can, to a large extent, be corrected with corticosteroid dosage equivalent to 5 to 15 mg. of prednisone daily.[35] This is one situation in which such steroids exert a net anabolic effect. Corticosteroids should not be used in place of other effective measures such as a gluten-free diet.

Chronic ulcerative colitis. If treated early and adequately (40 to 100 mg. of prednisone per day may be needed initially), the major manifestations of chronic ulcerative colitis can be suppressed. Remission can then be maintained indefinitely with relatively small doses of steroids.[24] If remission is complete, steroid therapy may be suspended indefinitely. If advanced pathologic changes have occurred, corticosteroids do not induce satisfactory remissions; in this situation, their chief value is as supportive therapy adjunctive to definitive surgical procedure. When the disease involves principally the distal colon, retention enemas containing steroid suspensions may be employed for maximal local effect with relatively less systemic effect than when the same dosage of steroid is administered orally.

Noninflammatory indications for corticosteroids

The "side effects" of anti-inflammatory steroids can be turned to advantage in the treatment of certain noninflammatory disorders.

Metastatic mammary carcinoma. Bilateral adrenalectomy has been used as a means of preventing adrenal estrogen secretion in patients with metastatic mammary carcinoma. The same objective can be achieved by the uninterrupted administration of ACTH-suppressing corticosteroids, e.g., 5 mg. prednisone every 8 hours. Larger doses are indicated in patients with hypercalcemia or symptomatic cerebral metastases.

Idiopathic hypoglycemia of infancy. Advantage is taken of the hyperglycemic action of corticosteroids in the treatment of idiopathic hypoglycemia of infancy. A sustained effect is required, and oral administration is often unreliable. The most satisfactory mode of treatment has been with approximately 15 mg. of methylprednisolone acetate intramuscularly every 4 to 5 days. Dosage should be adjusted in such a way that the blood sugar is not allowed to drop below 50 mg. per 100 ml. and clinical manifestations of hypoglycemia are totally prevented. The smallest amount of methylprednisolone that will achieve these results is recommended. Unfortunately, this method of preventing hypoglycemia is frequently attended by growth arrest resulting from the antianabolic action of the corticosteroid.

Virilizing congenital adrenal hyperplasia. In this disorder, the adrenocortical mechanism for synthesizing hydrocortisone is grossly inefficient, and a compensatory increase in ACTH secretion by the pituitary follows. Under the influence of high levels of ACTH, the adrenal cortices become hyperplastic and secrete large quantities of the androgenic byproducts of cortisol. Administration of hydrocortisone in physiologic amounts prevents the compensatory hypersecretion of ACTH, thus permitting involution of the adrenal glands and a decrease in secretion of androgenic byproducts to normal. This represents nothing more or less than substitution therapy, and undesirable effects should never be encountered because only physiologic amounts of the normal adrenal hormone are used.[7]

Shock. It is not uncommon for physicians and surgeons to use soluble hydrocortisone empirically in the treatment of hypotensive patients who fail to respond adequately to conventional measures for shock. Frequently, these patients respond with increases in blood pressure following hydrocortisone therapy. Probably, in many cases, the apparent therapeutic response is unrelated to the administration of the steroid. In some, the favorable response may be due to the fact that hydrocortisone increases the responsiveness of the vascular system to norepinephrine (endogenous or exogenous). In a few cases, the response to hydrocortisone is attributable to correction of a genuine deficiency of this hormone. Such a deficiency may be related to primary adrenal insufficiency, adrenal insufficiency secondary to hypopituitarism, or pituitary-adrenal unresponsiveness as a consequence of long-term corticosteroid therapy.

Spink[53] and Bein[3] have independently adduced evidence indicating the efficacy of massive doses of hydrocortisone and aldosterone, respectively, in maintaining vascular responsiveness to norepinephrine in endotoxin shock in the laboratory animal. This would seem to provide a rationale for the use of such steroids in certain types of clinical shock. It must be conceded, however, that there are no adequately controlled studies to demonstrate the efficacy of steroids in the management of shock in man.

Until critical clinical evidence is available, it would appear justifiable to continue empirical use of corticosteroids in treating clinical shock; a single dose of hydrocortisone is always harmless and may be lifesaving in an occasional patient. Once again, steroids should not be used as a substitute

for precise diagnosis and appropriate use of nonsteroidal therapy. Avoidable death from internal hemorrhage has been known to occur when blind reliance has been placed upon hydrocortisone to correct hypotension while the hematocrit determination was being neglected. In general, failure of any patient to respond to 100 mg. of soluble hydrocortisone every 4 hours should be regarded as evidence that adrenal insufficiency is not the cause.

Therapeutic limitations

The therapeutist is limited in the use of corticosteroids as anti-inflammatory agents by virtue of their many potential untoward effects. Certain groups of patients are more prone to develop unwanted effects than others. For example, patients who are very old, debilitated, or poorly nourished are especially likely to tolerate poorly the catabolic effects of large doses of corticosteroids. Supraphysiologic doses of corticosteroids will almost invariably cause growth retardation in children. Women show more readily than do men the changes in facial appearance and body habitus which are characteristic of Cushing's syndrome. Gonadectomized or postmenopausal women are especially prone to develop osteoporosis during treatment with corticosteroids. Latent diabetics may be converted into frank diabetics during corticosteroid therapy. Peptic ulcers may hemorrhage or perforate more readily during corticosteroid therapy. Because of the special dangers of corticosteroids in the above groups of patients, it is imperative that the therapeutic indications be clear cut and that the dosage be kept as low as is consistent with achieving therapeutic objectives.

One should be reluctant to initiate steroid therapy for more than emergency purposes in patients who have infections for which specific antibiotic therapy is not available. Even when specific antibiotic therapy is available, one should not lightheartedly undertake steroid therapy unless the therapeutic indications are compelling.

Therapeutic virtuosity

The art of therapy aims at the attainment of the greatest possible benefit with a minimum of undesirable effects from the use of various measures, medicinal and otherwise. The expert therapeutist must understand thoroughly both his patient and his drugs. In order to attain desirable effects while avoiding undesirable effects of corticosteroids, one must consider selection of steroid, route of administration, dosage, and duration of therapy.

For those who do not have the time to keep abreast of all clinically useful steroids and their proprietary names, it may be wise to become familiar with one preparation and use it consistently. If proper adjustment of dosage is considered, one may use dexamethasone, prednisone, prednisolone, and methylprednisolone interchangeably since they are qualitatively indistinguishable.

While short-term therapy is relatively free of complications, it must be recognized that there is some risk of incurring a long-term commitment when one is treating a chronic disease such as rheumatoid arthritis or intractable bronchial asthma. What may begin as short-term therapy might easily end as long-term therapy in such patients.

Nonsteroidal therapeutic measures should not be abandoned, even though the temptation to do so may be strong when the patient learns that steroids confer dramatic relief whereas his conservative regimen entailed much effort with only modest symptomatic benefit.

Some of the principal untoward effects of corticosteroids can be treated prophylactically and thereby minimized. For example, the patient receiving long-term steroids might well be put on a regimen which would be suitable for a patient with known peptic ulcer. This can be done as well before the ulcer actually develops as after.

In an attempt to forestall the development of catabolic complications such as osteoporosis, patients might be placed on a

relatively high protein intake and small doses of anabolic steroids.[49] Of course, one must not be too ambitious with anabolic steroid therapy in women and children.[39] In postmenopausal women, it may be possible to supplement small doses of androgens with estrogens. In children, doses of androgen large enough to cause sexual maturation and premature epiphyseal closure must be scrupulously avoided.

In patients who develop hyperglycemia during corticosteroid therapy, the judicious use of insulin, oral hypoglycemic agents, and dietary regulation is recommended.

The patient receiving large doses of corticosteroids must be carefully observed for development of infection, the signs of which may be somewhat obscured by steroid therapy. Prophylactic measures (but not prophylactic antibiotics) should be employed whenever possible. These measures include avoidance of exposure to infection, avoidance of skin injury, careful cleansing of the skin, and early use of topical bactericidal preparations whenever skin infections develop. Periodic chest x-rays (every 6 months) should be obtained for evidence of activation of tuberculosis. In the event that an infection does appear, it is imperative that the pathogenic organism be identified. If the organism is sensitive to antibiotics, these agents should be employed in fully effective dosage until the infection has been eradicated. Under these conditions, it is safe to continue treatment with corticosteroids. On the other hand, if the infecting organism is not sensitive to antibiotics, one may be obliged to discontinue steroids or to taper the dosage to physiologic levels until the infection can be controlled by natural immune mechanisms.

Abrupt withdrawal of corticosteroids may result in manifestations simulating adrenal insufficiency and in exacerbation of inflammatory processes. Gradual withdrawal is, therefore, common practice. If rapid reduction of dosage is indicated, it can be accomplished safely with decrements of 50 per cent in dosage on successive days until physiologic levels are reached. If slower reduction of dosage is indicated, e.g., when an attempt is being made to discontinue long-term therapy without a flare in symptoms in a patient with arthritis, each week the daily dose may be decreased by an amount of steroid equivalent to 1 mg. of prednisone. At the time steroids are discontinued, corticotropin may be given for several days in order to help restore adrenocortical responsiveness to endogenous ACTH. However, both the necessity and the efficacy of this measure are open to question.[19]

With prolonged steroid therapy, pituitary-adrenal responsiveness is impaired, and clinical adrenal insufficiency may develop under conditions of stress, for example, surgical operations, unless adequate quantities of hydrocortisone are administered. The possible need for such emergency treatment should be kept in mind for several months after termination of a prolonged course of corticosteroid therapy.

It is sometimes necessary to be reminded that in the treatment of Addison's disease, hypopituitarism, or virilizing congenital adrenal hyperplasia, corticosteroids have no untoward effects because they are employed only in physiologic doses. In these situations, the hazard is not in administering steroids but in withholding them.

In the past, corticosteroid therapy has sometimes gained a poor reputation because physicians have made errors in selection of patients and choice of dosage. Such errors have resulted in the occurrence of untoward effects out of proportion to therapeutic benefits and have led to unwarranted disenchantment with corticosteroid therapy per se. It is to be hoped that with increasing skill in the use of corticosteroids, the benefits will consistently outweigh the penalties of therapy.

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Clinical pharmacology of vasodilating drugs

The human pharmacology of vasodilators and their total cardiovascular effect are reviewed. Emphasis is placed on the peripheral circulation through skin and muscle; cardiac output, blood pressure, and circulation through the lungs, kidneys, liver, eyes, and splanchnic areas are also surveyed. Objective methods for studying the vasodilators in man are described in sufficient detail to make objective evaluation understandable. Laboratory studies are examined in the light of clinical observations, and the combined information serves as a basis for establishing indications for the use of these drugs.

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The large number and varied mechanisms of action of peripheral vasodilators make a thorough survey of their human pharmacology desirable. Since the behavior of the peripheral circulation in animals and man often differs, human studies are essential, and animal studies will be cited only when data on humans are not available. The results of acute experiments with these agents will be described, although it is realized that chronic administration may show results which differ from acute studies: for example, the dihydro alkaloids of ergot elicit certain responses in the wall of the blood vessel only when given for a long time.[94, 140, 153] These results differ from those seen soon after the acute administration of the drug.

The inadequacy of the term general vasodilator deserves comment. Detailed examination of the action of each of these drugs reveals that no therapeutically useful general vasodilator exists and that organ or region specificity may occur. It would be better to speak of skin or muscle vasodilators; however, even this is inaccurate in view of the different vascular reactions which can occur in various parts of a single organ. Organ specificity is shown by tolazoline and the dihydro alkaloids of ergot, which cause vasodilatation of all the skin, thus increasing the skin temperature of fingers and toes, but decrease the circulation through the gastrocnemius muscle.[88] However, nylidrin increases circulation through the gastrocnemius with little effect on circulation through skin of the fingers and toes. Region specificity is shown by β-pyridylcarbinol, which induces vasodilatation in the skin of the face and arms but at times vasoconstriction in the skin of the toes.[165] Even physiologically produced substances are not general vasodilators, because their effects may vary in different vascular beds, e.g., epinephrine produces vasodilatation in resting muscle and vasoconstriction in skin.[10, 11] Vasoactive substances do not always have the same effect

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under different circumstances. An example is the effect of the dihydro alkaloids of ergot, which are dilators when the cerebral vasoconstrictor center is active but are constrictors when the center has previously been depressed.[155]

Actions

There are many reasons for the selective vasodilatation of vasoactive drugs. Differences in the level of tonic activity cause selective vasodilatation, and it can be shown that interruption of those sympathetic nerves which maintain tonic constriction of skin blood vessels of the acra results in a large increase in skin circulation in these areas. Reflex body heating results in inhibition of the sympathetic nervous system and an increase in acral skin circulation when the nervous system is intact, but not after sympathectomy. The muscle beds possess relatively few sympathetic fibers, so that reflex body heating and sympathectomy have little effect on this circulation. It is therefore apparent that vasoactive drugs have diverse actions and that their effects must be measured in man, in both health and disease, in skin, muscle, kidney, liver, splanchnic areas, heart, lungs, eye, and brain if their actions are to be understood. Also, knowledge of vasomotor tone, nutritional and shunt circulation, and factors affecting flow locally in various peripheral vascular beds, as well as of the central circulation, is required to make the understanding complete.

Vasomotor tone. The peripheral blood vessels are normally in a state of partial constriction, and this is called vasomotor tone. The caliber of the vessels at any moment is the net result of dilating and constricting forces which are of nervous, hormonal, metabolic, and environmental origin. Vasomotor tone is also modified by drugs and disease. The autonomic nervous system and the chromaffin tissue situated in the adrenal medulla and elsewhere influence vasomotor tone largely by liberating epinephrine, norepinephrine, and acetylcholine, with characteristic effects in various vascular beds. In addition vasomotor tone is regulated by the release of hormones from the pituitary, thyroid, and adrenal cortex. Likewise, histamine, carbon dioxide, hypoxia, environmental temperature, and local tissue activity alter vasomotor tone.

Nutritional and shunt circulation. A characteristic of the circulation of the skin, and perhaps of muscle, is the presence of arteriovenous shunts between the larger vessels (arteries, arterioles, and venules). These shunts, which are proximal to the capillaries, are capable of dilating to a much larger diameter than capillaries; thus blood flow through the terminal vascular bed may be redistributed. The shunt circulation is controlled in large part by the sympathetic nervous system. Reflex body heating, which depresses sympathetic activity, raises the skin temperature of the fingers by increasing shunt flow, and therefore warm extremities and a large blood flow do not necessarily indicate better nutrition of the tissues. Body temperature is probably regulated to some extent by the diversion of large amounts of blood to the skin surface, from which heat is radiated to the environment. Barany[9] has shown that the acral skin circulation of diabetic patients increases significantly after sympathetic nerve block as shown by a calorimetric method which measures total skin flow (shunt and capillary), although the clearance of radioactive iodine from the skin is little influenced. In skin, therefore, an increase of shunt flow does not necessarily influence flow through the capillaries.

Blood flow in various vascular beds. The vascular system may be considered to be a group of circuits in which capillaries make connections between the arteries and veins and can be compared with an electric circuit in which resistors are in parallel. Arterioles on the afferent side of the capillaries are capable of large changes in caliber and regulate resistance in any one of the circuits. The arterioles regulate the rate at which blood flows out of the large

arteries and therefore regulate the volume of blood, pressure, and flow in the capillaries; these factors, in turn, determine the rate of interchange of fluids between capillaries and tissues. Fig. 1 shows the general plan of the circulation at rest. All of the blood passes through the right ventricle, lungs, left ventricle, and aorta, and all returns through the vena cava to the right side of the heart. Only a portion of the blood circulates through each of the various capillary circuits. The largest fraction flows through the splanchnic system and liver and smaller amounts flow through the kidneys, muscles, brain, skin, and coronary arteries.

The relative functional vascularity of the various organs is illustrated in Fig. 2, which shows the rate of blood flow in milliliters per minute per 100 Gm. of tissue through various vascular areas, at rest and with exercise. The kidneys, adrenal glands, thyroid gland, and lungs are well perfused at rest when compared with the skin and muscles of the extremities. The circulation changes markedly during exercise, increasing in the heart, lungs, muscles, and skin but decreasing in the kidneys and liver.

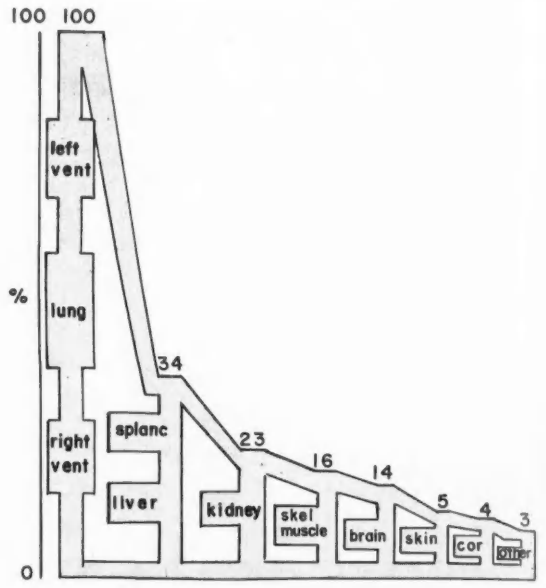


Fig. 1. General plan of the circulation at rest. One hundred per cent of the blood passes through the heart and the lungs, but only a portion circulates through each of the various capillary circuits.

Methods of study

The important methods used for studying the circulation in man will be discussed only briefly; a detailed description may be found elsewhere.[22, 190] Adequate methods are available for studying blood flow in skin, muscle, heart, kidney, eye, brain, liver, and splanchnic system.

Skin. The skin circulation may be evaluated by one or more of at least six methods: plethysmography, calorimetry, thermometry, heat flow methods, tissue clearance, and pulse recording.

Plethysmography. This is an ideal technique for studies of the digital circulation, blood flow being determined by the venous occlusion technique. In order to measure flow accurately, it is necessary to use a volume recorder. It is our opinion that a venous congestion test is necessary to establish an accurate measure of flow; amplitude or other characteristics of the volume pulse curve can, at best, give an approximation. Skin flow is measured in any one of the fingers or toes with the occluding cuff close to the proximal end of the digit; measuring the toes may cause difficulty at times, the fingers should not. As an alternative, skin flow may be measured by using the whole hand or foot, with venous occluding cuffs placed close to the detector at the wrist or ankle. Results agree well with direct methods such as the electromagnetic flow meter[33] and bleeding[11] and with indirect methods such as calorimetry[34] and dye dilution studies.[4, 52] Rheoplethysmography, a modification of conventional venous occlusion plethysmography, makes possible determination of the rate of blood flow into and out of a digit during a single pulse cycle. Under special circumstances, this technique is used to show the sites of action of vasodilatating drugs which affect inflow or outflow of a capillary bed.[23, 24]

Calorimetry. This method utilized extensively by some investigators[71, 125, 172] is

usually used on a finger. The technique involves measurement of heat exchange between a digit and a water bath maintained at a temperature of 5° C. (or more) below that of the body. When a state of equilibrium has been reached and the temperatures of the arriving arterial and departing venous bloods are known, the rate of blood flow can be calculated by using the Fick principle. It is then possible to calculate the smallest quantity of blood which could have conveyed the measured quantity of heat to the calorimeter. The conventional calorimetric method has been simplified by using a copper-tellurium-copper heat flow disk method[84]: the device used generates an electric potential which is proportional to the difference in temperature between its surfaces and therefore to the rate of heat flow between them; it also allows evaluation of local differences in the circulation by a method almost as simple as measurement of skin temperature but which is more nearly proportional to blood flow.[28]

Thermometry. Temperature measurements of the skin are convenient for estimating skin circulation; multichannel thermistor thermometers or thermocouples make it possible to sample numerous skin areas and to obtain patterns of response to various vasodilators.[188] The forehead, fingers, umbilicus, and toes are common sites used in measurement. Temperature gradients normally exist between umbilicus and fingers and along an extremity. The gradient may be diminished or abolished by certain peripheral vasodilators.[188] Simple skin temperature measurements are not reliable guides to blood flow over the entire flow range, as shown by comparisons with plethysmographic and calorimetric methods: under controlled conditions, however, there is a fairly linear relationship between blood flow as measured by the venous congestion test and skin temperatures between 30° and 35° C. Outside this range, the relationship is poor[190]: with changes of skin temperature from 25° to 30° C., very little increase in blood flow takes place, but changes from 35° to 36° C. are associated with large changes in blood flow as measured plethysmographically. Burton[25] has made measurements of skin temperature more meaningful in terms of blood flow by calculating a thermal circulation index: this calculation involves measurement or assumption of a rectal temperature of 37° C. and measurement of skin and room temperatures; the percentage change of the circulation from the control state is thus determined, and it shows a close relationship to changes in blood flow.

Heat flow method. Hensel[87, 88] has modified the skin temperature procedure by using a heat flow method to give qualitative information of skin flow; the method records differences of temperature between two identical bodies placed on the skin; one of these is a heater and the other a heat detector. Differences in the tempera-

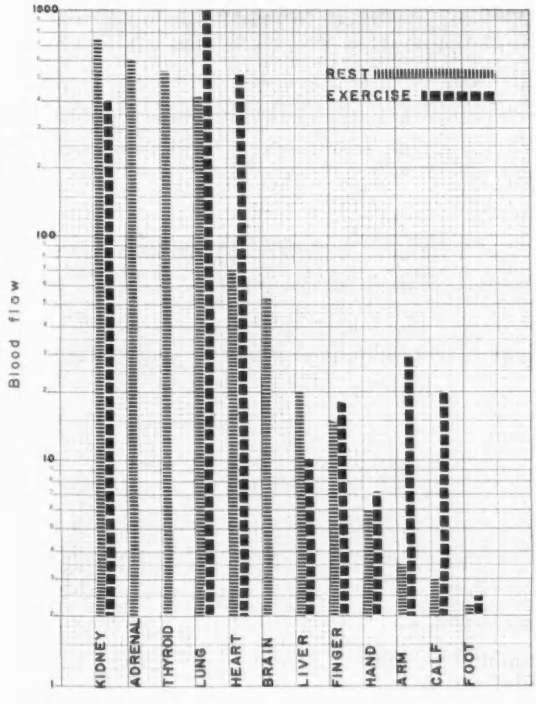


Fig. 2. Rate of blood flow through vascular areas at rest and after exercise. With exercise, increases in circulation occur through the heart, lungs, muscles, and skin, with decreases through the kidney and liver.

ture of the two depend on the coefficient of thermal conductivity of the tissue, and this is related to blood flow. The magnitude and variations of these changes are registered on an appropriate recorder.

Tissue clearance. Skin circulation can be assessed by using tissue clearance techniques, such as described by Kety[110] and used extensively by Hyman and his associates.[96-98] Radioactive sodium (Na^{24}) or iodine (I^{131}) is injected into the skin, and appropriate detectors and recorders provide an estimate of nutritional or capillary blood flow.[13] This technique does not record total blood flow as measured plethysmographically; shunt flow may at times be large compared to nutritional flow.

Pulse recorders. This method, studied extensively by Hertzman,[89, 90] makes use of light reflected from the surface of the skin into a phototube. With each pulse beat, variations of current are produced which are amplified and recorded. The amount of light which reaches the phototube varies with the flow of blood in the skin, and the height of the pulse waves is compared with an electric calibration. The changes in the potential of the light-sensitive cell depend on the amount of light absorbed by the tissues and on the ratio of oxyhemoglobin to reduced hemoglobin (color of the blood) as well as on the amount of blood in the tissues. The amplitude of the pulse under certain conditions is related to the arterial flow in the skin, and relative, qualitative changes of the skin circulation can be recorded before and after giving vasoactive drugs.

In the impedance plethysmographic technique, recordings are made of pulse waves which are roughly proportional to the changes of volume of the affected part. This method is not suitable for use with the venous occlusion technique since results are lower than those obtained with other, standardized volume plethysmographs.[190] Measurements of blood flow as derived from some characteristic of the pulse wave are uncertain in man in various disease states.

Muscle circulation. The methods used are a walk test for intermittent claudication, plethysmography, calorimetry, and arteriovenous oxygen differences.

Walk test. In this, the simplest test for determining adequacy of muscle circulation, the time taken to the onset of pain on walking is used for the evaluation of intermittent claudication.

Plethysmography. The classic instrument for the study of muscle circulation is the venous occlusion plethysmograph as used by Hewlett and van Zwaluwenburg,[91] Barcroft,[11] and Abramson.[1] This method has recently been modified using a triple pneumatic cuff technique allowing measurements to be made easily and quickly[100]; the circulation as measured by the rate of volume change of a limb after venous occlusion has been found accurate when checked against other techniques.[4, 11, 33, 34] To measure muscle flow in the forearm or calf with the triple cuff technique, the recording plethysmographic cuff is placed on the limb with low pressure and is used to detect change of volume. An arterial occlusion tourniquet is placed distal to the detecting cuff to prevent circulation through the hand or foot (which is largely through the skin). A venous occlusion cuff is placed proximal to the detecting cuff and is quickly inflated to about 60 mm. Hg. As a result, the segment of tissue under the detecting cuff increases in volume at a rate which can be determined from the record. The assumption is usually made that the rate of change of volume represents primarily blood flow through muscle and that the change of volume due to blood flow through skin is insignificant. There are, however, exceptions; for example, body heating produces reflex changes almost exclusively in skin vessels without significant changes in muscle circulation, while exercise has the reverse effect. Nevertheless, results obtained are satisfactory for measuring muscle circulation in man.

Calorimetry. The conventional calorimetric method can be used to study the slow effects of drugs on muscle flow but

cannot follow rapid changes which are often important in studying epinephrine, norepinephrine, bradykinin, acetylcholine, and similar drugs. Recently, Hensel[88] described a heat flow method employing a calorimetersonde for measuring blood flow in muscle: the instrument consists of a hypodermic needle of 1 mm. external diameter, at the tip of which is a heating element. On the shaft of the needle and 1 cm. from it, there is a heat-sensing element. The needle is inserted into a muscle and the difference in temperature between the heating and sensing bodies recorded; this depends on the coefficient of thermal conductivity of the tissue between them and is determined by the rate of blood flow. This method has been used extensively for studying the relationship between skin and muscle circulation with drugs such as tolazoline and nylidrin.[88] The technique has the disadvantages of requiring puncture of the muscle with a large needle, pain, reflex changes associated with the puncture, and altered conditions of the muscle; the precise location of the sensitive elements is important since it functions properly only when a large vessel is present between the heater and detector. Continuous recording of changes in muscle circulation is a big advantage.

Arteriovenous oxygen differences. Arterial oxygen saturation is determined after brachial artery puncture and venous oxygen saturation following insertion of a catheter into a deep vein which drains muscle. Theoretically, arteriovenous shunt flow should be inversely proportional to the arteriovenous difference. Interpretation of these data is complicated, and muscle clearance or other methods are necessary to differentiate shunt from nutritional circulation.

Heart. Cardiac output can accurately be measured by cardiac catheterization and by using the Fick principle. Although less accurate, curves obtained by an intravenous injection of I^{131}-tagged albumin and readings taken over the heart with a scintillation counter often give useful information. The ballistocardiograph, for example, as obtained on the standardized, low frequency Nickerson bed, gives useful information about the force of cardiac contraction before and after administration of drugs. X-ray kymograms taken before and after administration of vasodilators give qualitative information about cardiac output.

Kidney. The renal circulation may be assessed by *p*-aminohippuric acid clearance, from which renal plasma flow can be determined; this may be carried out simultaneously with measurements of the peripheral circulation.

Eye. Circulation of the eye may be studied qualitatively. Still photographs of the scleral vessels before and after administration of a drug may show dilatation or constriction; however, the rate of flow is not recorded. Estimates of linear flow rates of the scleral circulation can be made by the use of color movies. Angioscotometry, in which blind spots produced by blood vessels or perivascular exudates are mapped with appropriate equipment, may help in the evaluation of vasoactive drugs since the scotomas become bigger after administration of vasodilators. Linear flow rates cannot be studied with this method.[171] Subjective information about the retinal circulation can be obtained from the entoptoscope; the entoptic (Scheerer's) phenomenon is the visualization of one's own retinal circulation while gazing into a blue field. The entoptoscope provides a blue field into which the subject peers, observing his own retinal circulation as moving white specks. Changes in diameter of vessels and rates of flow can be estimated by the observer after administration of vasoactive drugs.[30, 143] The electroretinograph is an instrument which records electrical activity of the eye, and this may at times be related to blood flow.[102]

Brain. Cerebral blood flow was initially measured by Kety and Schmidt[109, 111] using the nitrous oxide method, and this has become the standard technique in man. The method involves intermittent sampling of

blood from a superior jugular bulb and a peripheral artery during a 10 minute period of nitrous oxide inhalation. Measurements are made of the average rate of blood flow per unit of brain for a 10 minute period of time. Cerebral blood flow is calculated from an equation based on the Fick principle. Although modifications of the original principle have been developed to simplify the technique,[113, 117, 162] the method has the disadvantage of requiring a trained technical team and arterial and venous punctures.

Liver. Liver blood flow can be measured by venous catheterization.[53] The catheter has made it possible to obtain blood directly from the hepatic vein and to apply the Fick principle to the measurement of liver blood flow. The rate of liver blood flow is given by the rate at which the liver adds or removes a test substance from the blood divided by the hepatic arteriovenous difference. Urea, sulfobromophthalein, and rose bengal have been used.[18, 119, 132, 159] The assumptions are as follows: the removal of dye from the blood depends solely on hepatic uptake; the arterial blood concentration of the dye at the point of sampling is the concentration in the blood entering the liver, and the blood from a single hepatic vein is representative of the mixed venous-hepatic drainage. The procedure, although difficult, gives reasonable estimates of the hepatic circulation.[167]

Splanchnic system. The splanchnic circulation can be measured with the principles used for liver circulation.

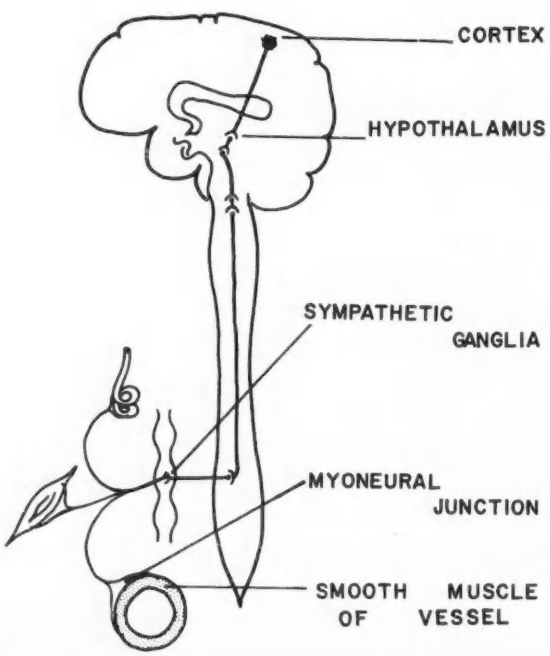


Fig. 3. Anatomic sites for vasoactive drugs.

Nervous control of blood vessels

Studies of the activity of the autonomic nervous system are of importance in evaluating vasoactive substances. The digital plethysmograph is ideally suited for studies of sympathetic nerve activity.[187] Certain stimuli such as sudden startling or an electric shock evoke sympathetic discharge resulting in constriction of digital arteries and veins. Absence of this reflex often signifies interference with sympathetic nerve activity. The plethysmogram also reveals the presence of slow volume changes (alpha and beta waves) in a digit, which are seen in normal subjects in a comfortable, warm environment. These, in part, represent variations of sympathetic nerve activity, and changes in these assist in defining the sites of action of drugs. The psychogalvanometer, which measures the electrical resistance of the skin between two points, such as the front and back of a digit, is also of importance in evaluating sympathetic activity. With a stimulus such as sudden startling, there is abrupt, transient sweating which lowers electrical resistance and is easily recorded with appropriate equipment. Ideally, studies of vasomotor tone and drug activity should include the simultaneous recording of vasomotor and sudomotor activity.

Sites of action of drugs

Vasodilators may be classified according to their sites of action, e.g., the cerebral cortex, hypothalamus, sympathetic ganglia, myoneural junctions, and smooth muscle of vessels (Fig. 3 and Table I). Some drugs, such as the dihydro ergot alkaloids, have more than one site of action.

Cerebral cortex. The influence of the cerebral cortex on the peripheral blood vessels is great. Vascular reactions resulting from emotional disturbances, e.g., the facial pallor of fear and pain and the blushing of embarrassment, are examples. Cortical lesions caused by trauma or tumor may result in vasomotor changes in the extremities. Anatomically, upper motor neurons originate in the premotor region of the cortex and synapse with neurons in the hypothalamus. It is not surprising, therefore, that sedative drugs such as the barbiturates and possibly some of the tranquilizers promote vasodilatation by inhibiting cerebral discharge to the hypothalamus. Vasodilators with a cortical site of action have not been studied in detail and are not yet clearly defined. It is not now possible to state which of the tranquilizers, sedatives, or hypnotics is most effective as a vasodilator; however, good vasodilatation can be achieved by controlling cortical activity with drugs or psychotherapy.

Hypothalamus. This is the brain area responsible for regulation of body temperature and partial control of peripheral vasomotion. Clinically, lesions of the hypothalamus result in hypothermia, hyperthermia, or poikilothermia, and any of these may be associated with flushing or cyanosis of the extremities. That the dihydro ergot alkaloids have a central site of action in the sympathetic system is inferred from the following: the alkaloids have an action on the brain because they are sedatives; there is no evidence that they block autonomic ganglia, and intravenous administration results in vasodilatation in a normally innervated limb but not in a sympathectomized limb.[17] Careful animal experiments have revealed the hypothalamus as the exact site of action.

Sympathetic ganglia. Neurons which originate in the hypothalamus pass to the vasomotor center in the medulla, decussate in the pons, and descend in the spinal cord. The sympathetic fibers lie immediately anterior to the pyramidal tracts and terminate in the lateral horns of the gray matter where they synapse with preganglionic neurons. With the possible exception of spinal anesthesia, vasodilators do not appear to block sympathetic nerve activity in these pathways. From the lateral horns of the gray matter, axons pass to sympathetic ganglia and the extremities. Preganglionic sympathetic neurons emerge from anterior roots as white rami communicantes and pass to paravertebral sympathetic ganglia. Postganglionic neurons leave paravertebral ganglia as gray rami communicantes and join spinal nerves which are distributed to blood vessels, sweat glands, and pilomotor muscles.

Numerous drugs capable of blocking the paravertebral sympathetic ganglia are available. These drugs have no sedative or central effect and have no direct action on the smooth muscle of blood vessels. Sympathetic block is shown by suppression of

Table I. *Sites of action of agents which have vasodilating properties*

Site	*Agent*
Cortex	Barbiturates
Hypothalamus	Dihydro ergot alkaloids
Sympathetic ganglia	Ganglion-blocking agents Tetraethylammonium chloride Camphorsulfonate Mecamylamine Trimethidinium Pentolinium Hexamethonium Chlorisondamine Pendiomide SC-1950 (dimethyldiethylpiperidinium bromide)
Myoneural junction	Adrenergic blocking agents Azapetine Phenoxybenzamine Dihydro ergot alkaloids Tolazoline Phentolamine
Smooth muscle of vessels	Direct-acting drugs β-Pyridylcarbinol Nicotinic acid Cyclandelate Nylidrin Isoxsuprine

digital vasoconstriction to an electric shock, development of Horner's syndrome, and failure of postural vasomotor reflexes to maintain blood pressure in the upright position. Vasodilatation occurs in the acral skin areas, and sweating is decreased. Since the drugs are not adrenolytic, injection of epinephrine results in normal elevation of blood pressure or even an exaggerated rise because of epinephrine sensitivity or altered amine oxidase activity which follows ganglionic block. The parasympatholytic effect which accompanies ganglionic block is shown by slowing of gastric motility, dryness of the mouth, achlorhydria, and loss of accommodation. Most of these findings can be reversed by the injection of neostigmine. In animals, ganglionic blockade is readily shown by electrical stimulation of preganglionic nerve fibers and by recording the effect on the nictitating membrane or other end organs. Ganglion-blocking drugs have limited value in the treatment of peripheral vascular disease because of their profound effect on blood pressure which precedes significant peripheral vasodilatation and because undesirable effects result from parasympathetic as well as sympathetic block.

Myoneural junction. Drugs acting on the myoneural junction are important in the treatment of peripheral vascular disease because sympathetic nerve activity can be interrupted without affecting the parasympathetic nervous system. These drugs, for the most part adrenergic blocking agents, are listed in Table I. The adrenergic blocking agents are those which inhibit or reverse some of the actions of injected epinephrine. Ordinarily, when administered intravenously, epinephrine increases cardiac output, raises blood sugar, produces tremor, constricts blood vessels of certain skin areas such as the face, fingers, and toes, increases systolic blood pressure with little change or a fall of diastolic pressure, and induces ectopic ventricular beats.

Drugs are usually classified as adrenergic blocking agents according to their ability to inhibit or reverse the effect of epinephrine on blood pressure; Goetz and Katz[6] demonstrated this well: after administration of the dihydro alkaloids of ergot, epinephrine caused a fall of systolic and diastolic blood pressure. One must distinguish between adrenergic blocking and sympatholytic drugs: characteristically, adrenergic blocking drugs reverse the effect of injected epinephrine at lower doses than are required to block sympathetic reflexes. The ganglion-blocking drugs are sympatholytic and are often without adrenergic blocking properties. A number of orally effective adrenergic blocking drugs are available; these combat epinephrine-induced systolic hypertension and control some of the symptoms of epinephrine excess.

Direct action on smooth muscle of vessels. Drugs probably exerting a direct action on smooth muscle of vessels (Table I) are effective in the treatment of peripheral vascular disease. These drugs fall into two classes, those which dilate skin vessels and those which dilate muscle vessels. The site of action can easily be demonstrated by intra-arterial injection into a sympathectomized limb and recording of skin and muscle circulation; these drugs are without adrenergic blocking properties, do not block sympathetic and parasympathetic ganglia, and have no effect on the hypothalamus or cortex.

Pharmacologic properties of vasodilators

The classes of drugs discussed are the hypothalamic ganglion-blocking and adrenergic blocking agents and the direct-acting drugs (Table I). Examples of each of these groups will be discussed in detail.

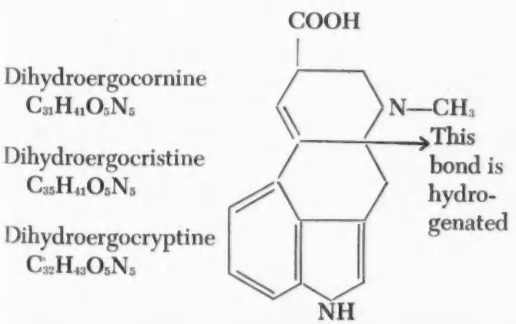
Dihydro ergot alkaloids. Knowledge of the ergot alkaloids has developed slowly since the isolation of ergotamine by Stoll in 1918.[173] In 1943, a series of dihydro alkaloids was prepared by hydrogenation of one of the double bonds in the lysergic acid portion of the ergot molecule. A mixture of dihydroergocornine, dihydroergocristine, and dihydroergocryptine which has been

studied extensively has adrenosympatholytic, central sedative, and bradycardic actions and is suitable for oral, subcutaneous, intravenous, intramuscular, and intra-arterial administration.

Peripheral effects. The peripheral vasodilator action is due largely to sympathetic block and adrenolytic action; thus, peripheral vasodilatation occurs when sympathetic tone is high or epinephrine levels are increased (Fig. 4).

Adrenolytic effects. There is substantial evidence showing adrenergic block. The usual increase in metabolic rate and blood sugar after epinephrine is inhibited.[154] In hypertensive subjects given large parenteral doses of the alkaloids, epinephrine causes a fall of systolic blood pressure rather than a rise.[62] Ventricular fibrillation and ventricular ectopic beats caused by cyclopropane are less frequent after premedication with the dihydro alkaloids. Renal ischemia caused by epinephrine, asphyxia, or electrical stimulation of splanchnic nerves can be relieved with the dihydro alkaloids. Pretreatment of animals increases the lethal dose of epinephrine by approximately 300 times.[155] However, the vasodilatation in muscle usually seen when epinephrine is infused into an isolated limb is not reversed by the alkaloids, and their failure to inhibit the positive inotropic effect of epinephrine on the isolated heart in situ are not consistent with adrenolytic activity.

Sympatholytic effects. In man, the sympatholytic effect of the dihydro alkaloids usually appears at lower doses than are required for adrenergic block. The increase of blood pressure which usually follows the Valsalva maneuver is blocked,[107] as is the hypertensive reaction which follows immersion of the hand in cold water.[185, 189] Vasoconstriction caused by smoking is inhibited,[107] and postural hypotension is common.[56] Spontaneous vasomotor changes of the fingertips and the vasoconstriction usually following inspiration and sudden exposure to bright light or pain are inhibited.[186, 189]



Dihydro ergot alkaloids

Heart. In patients with a normal cardiac output, administration of the dihydro alkaloids leaves the stroke volume unchanged, but pulse rate decreases; blood pressure falls mainly because of peripheral vasodilatation. When cardiac output has been increased by epinephrine, the drugs decrease the stroke volume, cardiac output, and blood pressure because of decreased cardiac rate and peripheral vasodilatation. There is probably little influence on the coronary circulation.[85, 164, 174] Systolic blood pressure falls more than diastolic when large doses have been given. The venous pressure increases slightly as a result of arteriolar dilatation in the periphery.[41]

Brain. The dihydro alkaloids have a sedative action[145] and potentiate the effects of barbiturates; there is central inhibition of pressor receptor reflexes[154]; bradycardia is of central origin,[29, 185] and this is partially blocked by atropine,[185] indicating an increased vagal tone; the central depression of vascular tone has been well documented[156]; body temperature falls, probably because of peripheral vasodilatation. The effect of these alkaloids on increased cerebrovascular resistance in hypertensive patients is significant; however, normal cerebrovascular resistance is not decreased.[78, 79]

Kidney. Renal plasma flow decreases considerably with the initial fall of blood pressure but returns to normal while the lower blood pressure continues. The urine output is decreased.

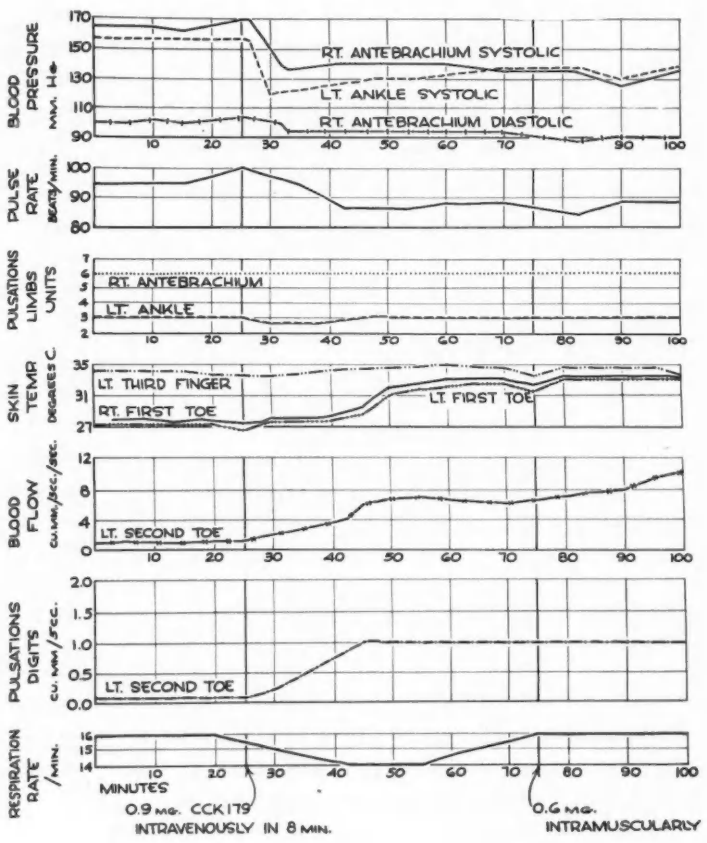


Fig. 4. Peripheral vasodilating and other physiologic responses to the dihydro ergot alkaloids.

Liver. The blood flow decreases with the initial fall of blood pressure but returns to normal although blood pressure continues to be low.[185]

Doses. Average doses are 5 mg. orally, 0.5 mg. sublingually, 0.6 mg. subcutaneously, 0.3 mg. intravenously, and 0.3 mg. intra-arterially.

Toxicity. The most common untoward effects are nausea and vomiting. Nasal obstruction caused by dilatation of the vessels in the nasal mucous membrane may occur[185] but is not particularly disturbing and indicates that the dose has been adequate to produce the desired pharmacologic effects. Occasionally, headache, flushing, and urgency of micturition occur. Postural hypotension is not uncommon if the drug is given parenterally.[56, 185] Tachyphylaxia has not been reported.

Indications. The depression of the vasomotor center and pressor reflexes, as well as cardiac slowing resulting from vagal stimulation and peripheral adrenergic block, have led to application of the drug in patients with neurogenic hypertension due to increased irritability of the vasomotor center. Hypertensive headache and headache in patients with sympathotonia are occasionally relieved. The actions of reduced vascular tone, central sedation, and damping of the pressor reflexes are useful in the treatment of patients with hypertensive crises, and symptoms of hypertensive encephalopathy may be relieved because of a decrease of cerebrovascular tone. Tachycardia caused by epinephrine in anxiety states and Ménière's syndrome resulting from a vascular abnormality may be improved. A strong bradycardic effect may be induced in combination with digitalis, reserpine, or Veratrum alkaloids.

The peripheral vasodilator effects are variable and unpredictable, and the drug is a relatively poor dilator of skin vessels as shown in Fig. 5. Variability of response

depends on the level of circulating epinephrine and on the activity of the vasomotor center. The drug is of moderate value in the treatment of Raynaud's disease because of central sedative and mild vasdilator actions. It is less satisfactory for vascular disease of the lower limbs although healing of skin ulcers after frequent injections has been reported.

The dihydro alkaloids of ergot should probably be used in conjunction with other vasodilators such as azapetine to strengthen the adrenergic blocking effect. A combination of central depression of the vasomotor center by the dihydro alkaloids and strong peripheral adrenergic block by azapetine results in good peripheral vasodilatation.

Tetraethylammonium chloride. The ganglion-blocking drugs shown in Table I have not been widely used for the treatment of peripheral vascular disease. The parent drug, tetraethylammonium, is typical of drugs in this class.

Tetraethylammonium chloride, a quaternary ammonium compound first described by Atchison and Moe in 1945 and in 1946,[6, 7] blocks sympathetic and parasympathetic ganglia. It may be given by intramuscular, subcutaneous, or intravenous injection, but there is no oral preparation. Other ganglion blocking agents, such as mecamylamine and chlorisondamine, may be administered orally.

Peripheral vascular effects. Given intravenously, tetraethylammonium chloride significantly increases skin temperature and blood flow in fingers and toes but increases muscle circulation only slightly.[88] There is no effect in a sympathectomized limb, and since intra-arterial injection does not alter the circulation, there is no direct action on arterioles. The dose is critical, since small doses are relatively ineffective and large doses are associated with undesirable effects caused by sympathetic and parasympathetic block. Peripheral vasodilatation is increased by combining body heating with the administration of tetraethylammonium chloride.[66]

Cardiac output and blood pressure. Intravenous injection leads to a prompt increase of pulse rate, increase in the force of cardiac contraction as shown by ballistocardiography, and a fall in systolic and diastolic blood pressure which lasts for about an hour.[95]

Sympatholytic and parasympatholytic effects. Large doses cause orthostatic hypo-

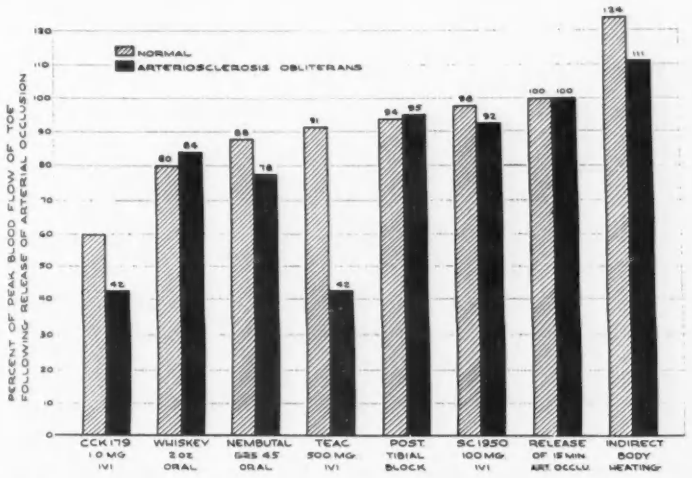


Fig. 5. Vasodilating effects of various agents on the circulation of the toe (skin) compared with reactive hyperemia produced by release of an arterial occluding tourniquet after 15 minutes of arterial obstruction. The maximum vasodilatation produced with this procedure is considered 100 per cent. The dihydro ergot alkaloids are relatively poor dilators. Tetraethylammonium chloride is a ganglion-blocking drug, and SC-1950 is an effective parenteral experimental ganglion-blocking agent.

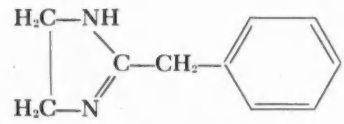
tension, inhibition of the Flack test, and abolition of digital vasomotor reflexes caused by inspiration, pain, startling, etc. The cold pressor reaction is reduced, and reflex sweating measured with the psychogalvanometer is inhibited; sympathetic block is shown by Horner's syndrome, hot and dry extremities, dilated veins, and impotence; parasympathetic block is shown by decreased volume and acidity of gastric secretion, inhibition of gastric motility, and distention of the intestines. The following are also seen: dry mouth and skin, flushed face, urinary retention, constipation, and blurred vision.

Epinephrine sensitivity. Administration of tetraethylammonium chloride increases sensitivity to circulating epinephrine similar to that seen after sympathectomy[55] and has been demonstrated in the general and renal circulations.[137, 138] The digital arterioles become more sensitive to both exogenous and endogenous epinephrine; epinephrine liberated during insulin hypoglycemia produces large changes in skin temperature.[43, 183]

Pulmonary circulation. In patients with primary pulmonary hypertension, pulmonary artery pressure and vascular resistance decrease and pulmonary blood flow increases after the intravenous injection of 400 mg.[44] A greater effect is obtained with tolazoline.

Indications and untoward effects. Ganglion-blocking drugs are not usually suitable for the treatment of ambulatory patients with peripheral vascular disease because of the high incidence of untoward effects and their epinephrine-sensitizing properties. However, in hospitalized patients, these drugs may be used in combination with adrenergic blocking drugs to increase peripheral skin circulation. They may also be used instead of nerve block for the evaluation of causalgia. Visceral pain, including that of angina pectoris, is blocked by tetraethylammonium chloride even though vasodilatation is moderate or slight. Untoward effects are postural hypotension, blurred vision, dry mouth, constipation, tachycardia, and impotence (*vide supra*).

Tolazoline. Tolazoline hydrochloride (benzazoline), first described in 1939, lowers blood pressure and dilates arteries. It has adrenolytic, sympatholytic, and direct histamine-like vasodilating actions and some sympathomimetic and parasympathomimetic properties. Its biologic halflife is about 2.5 hours, and it is excreted essentially unchanged in the urine.[20] Renal elimination of tolazoline is by tubular transport and glomerular filtration. Unlike β-chloroethyldibenzylamine and other adrenergic blocking drugs, tolazoline is not stored in adipose tissues, and this characteristic accounts for its relatively short duration of action compared to phenoxybenzamine.



Tolazoline

(2-Benzyl-2-imidazoline hydrochloride)

Peripheral vascular effects. Tolazoline dilates skin vessels of the extremities if the sympathetic nerves are intact[64, 95, 149]; however, large doses may produce some vasodilatation in a sympathectomized limb.[61] Given in a slow intravenous drip, it is a more effective skin vasodilator than tetraethylammonium chloride.[80, 127] Tolazoline does not improve muscle circulation, and the calorimetersonde has indicated decreased heat transfer in muscle.[88] Clearance of radioactive materials from muscle is decreased,[57] but muscle oxygen tension is increased.[166]

Cardiac output and blood pressure. A therapeutic dose does not increase cardiac output, but a large dose increases minute volume and cardiac rate,[76] and changes suggestive of increased cardiac output occur in the ballistocardiogram.[112] Blood pressure generally increases slightly, and at the same time, the volume pulse of fingers and toes increases.[61] Venous tone

is characteristically decreased, especially when it has previously been high, as in patients with poliomyelitis.[168]

Adrenolytic effects. In small doses, tolazoline is adrenolytic, and larger doses are required to block sympathetic reflexes.[74] Tolazoline prevents hyperglycemia induced by epinephrine,[67, 83] blocks the effect of norepinephrine, and is therefore used to prevent sloughing following accidental infiltration of norepinephrine into subcutaneous tissue.[139]

Sympatholytic effects. Large doses (200 mg. parenterally) block postural reflexes and suppress the cold pressor reaction and vasoconstrictor reflexes of the digit which follow inspiration.[61]

Pulmonary circulation. In patients with primary pulmonary hypertension or pulmonary hypertension caused by congenital heart disease, pulmonary artery pressure and vascular resistance decrease and pulmonary artery flow increases.[45] This effect on the pulmonary circulation is not seen in normal subjects; however, in pulmonary hypertension, there is selective reduction of pulmonary artery pressure with minimal change of systemic pressure.

Circulation of the eye. There is evidence that the circulation of the retina is improved in diabetics[31, 63]: the electroretinogram shows increased electrical activity, and this suggests increased circulation.[102, 116] Changes of conjunctival circulation can also be observed microscopically.[108]

Cerebral circulation. Nitrous oxide studies show slight cerebrovascular constriction and hypoxia after 50 mg. intravenously.[19, 32, 42, 163]

Splanchnic circulation. This is increased along with the increased circulation of the fingers and toes.[177]

Renal circulation. Renal function is improved in hypertensive patients.[176]

Untoward effects and tolerance. These are mild and not serious deterrents to the use of the drug. There is an antiejaculatory effect,[120] cardiac irregularities may develop with large doses,[121] coronary pain has been described,[38] and there is an increase of gastric acidity and motility. Pituitary extract is an effective antagonist. Tachyphylaxia does not develop.

Indications. The combination of adrenergic block and sympatholytic and direct action has made this a useful drug for the treatment of peripheral vascular diseases. The following conditions have been reported to be improved following use of tolazoline: porphyria,[179] frost bite,[47] hypertensive ischemic ulcers,[150] chilblains,[92] poliomyelitis,[168] acrodynia,[60] vasospasm from any cause,[65] scleroderma with functional vasoconstriction,[50] pheochromocytoma,[8] allergic angiitis,[124] vasoconstriction associated with herpes,[16] causalgia,[136] cutdown gangrene,[51] circulatory disturbances of the inner ear,[158] Raynaud's phenomenon, especially after sympathectomy,[135] pulmonary hypertension,[75] congestive heart failure,[182] arteriosclerosis obliterans with functional vasoconstriction,[114] vasoconstriction associated with diabetes,[80] functional dysmenorrhea,[73] skin ulcers due to ischemia of any cause,[37] diabetic retinitis,[160] and norepinephrine-induced tissue necrosis.[139]

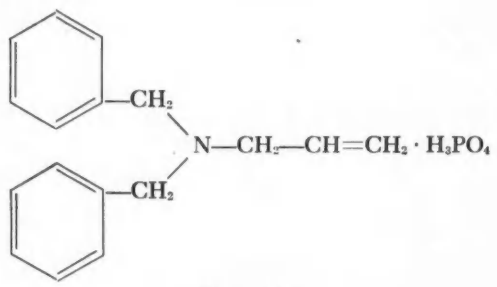
Dose. Tolazoline is given in doses of 25 mg. orally or intramuscularly, 50 mg. in a slow intravenous drip, or 15 mg. intra-arterially[118, 122, 142] or by iontophoresis.[175] It is advisable to start with 12.5 mg. three times a day after meals and increase after 1 week to 25 mg. three times a day. If this is well tolerated, one 80 mg. long-acting tablet is given once or twice a day. The long-acting tablet has advantages over the short-acting one. An effective vasodilating combination for hospitalized patients is made up of 25 to 50 mg. in 1,000 ml. of 5 per cent glucose with 5 per cent alcohol given intravenously. Additional vasodilatation can be produced by body heating.

Azapetine. Azapetine, first described by Wenner,[180] is, like tolazoline, a short-acting, adrenergic blocking drug with norepinephrine-blocking properties. It has many properties in common with benzylimidazoline and is the most potent of the eighteen dibenzazepine derivatives which have been synthesized. Azapetine is sympatholytic

and has a direct action on blood vessels.[129] It is given orally in a dose of 50 mg. three times a day after meals or intravenously at 1 mg. per kilogram of body weight in 250 ml. of normal saline in the course of 1 hour.

Peripheral effects. Blood flow through skin, as shown by skin temperature measurements,[65, 181] and through muscle[14, 178] is increased whether or not the vessels are innervated, and this suggests direct action on the vessels. The drug is effective in diseases of the upper and lower extremities.

Cardiac output and blood pressure. Effects on the heart are not striking. Green and DuBose[68] calculated that after administration of the drug, the circulatory index, which is an estimate of cardiac output based on heart rate and corrected pulse pressure, increased by 20 per cent and the pulse rate went up about 6 per cent over control values.



Azapetine

(6-Allyl-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine phosphate)

Azapetine, like papavarine, dilates the coronary arteries in animals.[146] After large doses, systolic and diastolic pressures fall, especially in the standing position; this does not, however, occur after therapeutic doses. The cardiac-stimulating action of the sympathomimetic amines is blocked by azapetine.[35]

Adrenolytic effects. Azapetine blocks the vasoconstrictor action of epinephrine, norepinephrine, phenylephrine, and sympathetic nerve stimulation in muscle and skin.[65, 69, 133] It prevents hyperglycemia resulting from stimulation of the sympathetic nervous system[123] and mesenteric vasoconstriction caused by norepinephrine and epinephrine.[39] It prevents the development of fibrillation of the dog heart caused by a mixture of chloroform and benzene given intratracheally or by epinephrine given intravenously. Like other adrenergic blocking agents, azapetine inhibits the excitatory actions of epinephrine and norepinephrine but does not influence inhibitory actions.

Sympatholytic effects. These appear with a slightly larger dose than that which produces adrenergic block. For example, the dose of azapetine which reverses the epinephrine effect on blood pressure only partially blocks the response of the nictitating membrane to electrical nerve stimulation. Azapetine is similar to the benzodioxane prosympal, which blocks the effects of epinephrine and of sympathetic nerve stimulation, but differs from piperoxan, which blocks the effects of sympathetic nerve stimulation only if large doses are administered, although small doses block the epinephrine effect.

Effects on sympathectomized limb. Long after sympathectomy, there is increased sensitivity of skin vessels to epinephrine,[72] and additional improvement results from the use of azapetine. Vasodilatation results whether sympathetic nerves are present or not.[65]

The ratio of the adrenolytic to the sympatholytic dose is a fundamental property of a compound and is related to the closeness of fit to epinephrine receptors. Whereas one compound can prevent the action only of circulating epinephrine at the receptors, another, having a more perfect fit to the receptor, may block both circulating epinephrine and the substance released at the sympathetic nerve endings. In this respect, azapetine may be considered as a specific competitor with epinephrine for the receptor surface.

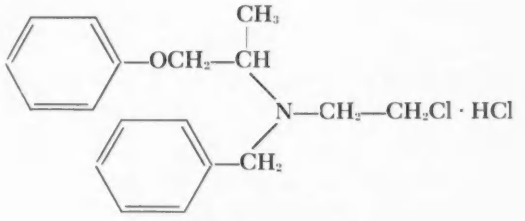
Renal circulation. In the presence of increased circulating epinephrine, azapetine decreases peripheral vascular resistance and increases renal plasma flow. In the presence of a somewhat lower blood pressure, renal flow is maintained after the ad-

ministration of azapetine, thus indicating decreased renal vascular resistance.[81, 169]

Untoward effects. The following, all relatively mild, have been reported: nausea, dizziness, syncope, drowsiness, diarrhea, burning skin, vomiting, headache, nervousness, nasal stuffiness, triple vision, blurred vision, trembling, drug fever, sweating, precordial pain, abdominal cramps, deafness, irritability, palpitation, hives, spontaneous voiding, and hot flashes.

Tachyphylaxia has not been reported.

Indications. Azapetine has been useful in the treatment of patients with vasospasm or vasoconstriction due to increased circulating epinephrine or increased sympathetic nervous system stimulation, also in arteriosclerosis and in the conditions in which tolazoline has been used *(vide supra).* It is an effective, well-tolerated vasodilator, especially when combined with others, such as tolazoline.



Phenoxybenzamine

(*N*-Phenoxyisopropyl-*N*-benzyl-β-chlorethylamine hydrochloride)

Phenoxybenzamine. Phenoxybenzamine hydrochloride, which is similar to azapetine and tolazoline, is an adrenergic blocking agent and does not affect the parasympathetic system. It blocks the neuroeffector junction if adrenergic mediators are involved in transmission of nerve impulses. Large doses produce adrenergic block and reversal of the pressor effects of injected epinephrine. It may be administered orally and parenterally, including intra-arterially.[46]

Peripheral effects. Large doses, for example 40 mg. per day, increase the skin temperature of the toes,[148] but the rise of temperature is moderate and untoward effects may occur. After an intravenous injection of 0.5 mg. per kilogram of body weight, a definite increase of blood flow to the foot has been measured plethysmographically.[193] Blood flow in muscle is probably increased.[40]

Adrenergic blocking and sympatholytic effects. Adrenergic block in man, as shown by orthostatic hypotension and orthostatic tachycardia, has been produced by 1 mg. per kilogram of body weight.[130] Phenoxybenzamine counteracts the adrenergic sensitivity which follows the use of ganglion-blocking drugs[12] and has been used successfully in the treatment of patients with pheochromocytoma.[3] It blocks sympathetic reflexes[148]: cold pressor response is partly or completely inhibited, and pressor response to the Valsalva maneuver is blocked in many cases; it also interferes with pressor response to phenylephrine.[130]

Cardiac output and blood pressure. Generally, cardiac rate increases, but cardiac stroke volume does not change.[95, 161] Arterial pressure falls.

Renal circulation. The renal circulation is not influenced significantly unless previously reduced by epinephrine.[86, 131]

Untoward effects. These are numerous and include weakness, nasal obstruction, postural hypotension, and disturbed vision. There is a strong antiejaculatory effect.[70, 120] There is a tendency for tolerance to the drug to develop.

Indications. Phenoxybenzamine has been used in the treatment of shock, hypoxic edema,[82] causalgia, and pheochromocytoma. It has been useful in most of the vascular diseases with sympathotonia or increased amounts of circulating epinephrine.

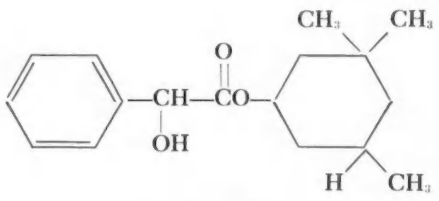
Phenoxybenzamine is less satisfactory than azapetine or tolazoline, and vasodilatation of toes and fingers in a cold environment is moderate and irregular.[65]

Phentolamine. Phentolamine is an adrenergic blocking drug which has been widely used in the diagnosis of chromaffin tumors; it is not particularly effective in patients with peripheral vascular disease. Phentolamine effectively blocks the sympathetic

nervous system at the receptor organs, reverses the normal hypertensive action of injected epinephrine, and prevents the pressor response to norepinephrine. It increases blood flow through the skin of the extremities in normal subjects and in patients with peripheral vascular disease. In large doses, it blocks the induced vasoconstrictive reflexes of the digits. There is little, if any, direct vasodilating effect on the vessel wall. In peripheral vascular disease, phentolamine is usually administered orally in doses of 30 mg. three or four times per day. It is a poor vasodilator compared to posterior tibial nerve block.

The untoward effects are diarrhea, nasal stuffiness, dizziness, nausea, vomiting, weakness, palpitation, chills, nervousness, dyspnea, vasomotor collapse, drowsiness, itching, and petechial rash.

Cyclandelate. Cyclandelate is a spasmolytic drug with an effect on peripheral smooth muscle. Funcke[15, 58] states that the mandelic acid esters of alcohols with 9 carbon atoms possess strong spasmolytic properties, and their effect on spasm of smooth muscle is more than twice as great as papaverine. Cyclandelate produces vasodilatation without interfering with the autonomic nervous system. The usual dose in man in 200 mg. orally four times per day.[157] After a large single dose, onset of action



Cyclandelate

(3, 3, 5-Trimethylcyclohexyl mandelate)

is about 15 minutes and duration is from 4 to 6 hours.

Cardiac output and blood pressure. There is no significant effect on cardiac output, pulse rate or blood pressure.[157] The electrocardiogram is not altered.

Peripheral effects. The circulation of the skin is improved in the acral areas according to Kappert.[106] Studies of the base of the nail with the capillary microscope show increased vascularity 15 to 30 minutes after a large single dose.[115] In patients with Raynaud's disease, there is rapid warming of the hands after removal from cold water.[106, 134] Plethysmography shows increased pulsations of fingers and toes, increased blood flow, and vasodilatation in sympathectomized limbs.[36, 106, 157]

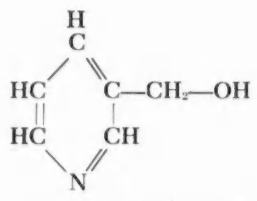
Muscle circulation. Walking ability is improved in patients with various vascular diseases, including arteriosclerosis obliterans and Buerger's disease,[106, 157] which suggests improvement in muscle circulation, but plethysmographic or clearance studies are not available.

Indications. Success has been reported in patients with Raynaud's disease, arteriosclerosis obliterans, diabetic vascular disease, thrombophlebitis, ischemic neuritis, night pain, organic and functional vascular disorders, thromboangiitis obliterans, and frost bite. It has been reported as useful for healing ulcers associated with the above diseases. Acrocyanosis has responded poorly.

Toxicity is low; with large doses, there may be flushing, tingling, sweating, nausea, or headache.

Cyclandelate has been used a great deal in Europe. It can probably be used effectively in combination with other vasodilators which have different sites of action. Little is known about possible alterations in the circulation of the brain, lung, kidney, liver, and other areas after administration.

β-Pyridylcarbinol. β-Pyridylcarbinol is a nicotinic alcohol. It has a direct vasodilating action on arteries, especially of the upper extremities. It produces its vasodila-



β-Pyridylcarbinol

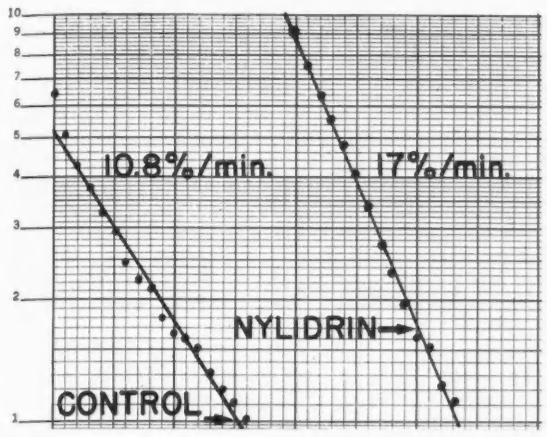


Fig. 6. Rate of clearance of I^{131} from calf muscle after administration of nylidrin compared with the control taken in the same patient before administration of the drug.

tation after conversion to nicotinic acid.[184] The short-acting form is given orally, 50 mg. after meals, producing some facial flushing; 150 mg. of the long-acting form after each meal produces less flushing.

Cardiac output and blood pressure. These are not changed when therapeutic doses are used.[67, 95]

Skin circulation. The effect on the circulation of the skin is variable, but there is often a slight increase in the temperature of the fingers without an increase in the temperature of the toes[67]; occasionally, however, it decreases. The forehead temperature characteristically increases by 1.5° to 2° C.[2] Vasodilatation has been noted in the skin of the face, neck, trunk, and proximal parts of the upper extremities at times with a decrease of skin temperatures of fingers and toes; this vasoconstriction is thought to represent thermoregulatory compensation for the cutaneous vasodilatation in the head and neck.

Circulation of muscle. Intermittent claudication has been improved subjectively in patients with peripheral arterial disease.[59] Abramson, Katzenstein, and Senior[2] made simultaneous plethysmographic and thermometric measurements of blood flow in an arm while environmental temperature was 22° C. A slight increase of the circulation was recorded by the plethysmograph, and the skin temperature remained unchanged. These authors state, "The finding of an increase in total flow through the forearm and the hand without any concomitant rise in skin temperature in these sites suggests that the predominating effect is not upon the cutaneous vessels but rather on those of the muscles." Few other studies of muscle circulation have been made.

Indications. The drug has been used in the treatment of chronic trench foot,[147] arteriosclerosis obliterans,[151] disturbances of the inner ear,[93] and vasospastic states.[67]

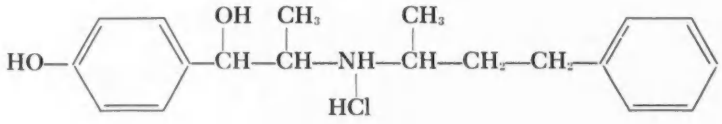
Untoward effects. Burning and stinging sensation in the head, face, and neck, flushing and tingling of the face, metallic taste in the mouth, burning of the eyes, headache, and mild epigastric pain have been reported. Orthostatic hypotension does not occur. If large doses are given for a long time, liver damage may occur. Large doses lower the level of the blood cholesterol.[191]

β-Pyridylcarbinol is probably a relatively poor vasodilator of skin and muscles of the extremities but a better vasodilator of the skin of the head and neck. The combination of vasodilatation and the ability

Table II. *Effects of various agents and procedures on peripheral skin and muscle flow in man*

Procedure	*Flow**	
	Skin	*Muscle*
Resting blood flow	2.1	1.5
Reactive hyperemia	18.0	15.0
Sympathectomy	12.4	1.8
Reflex heat	8.8	1.6
Exercise	3.8	8.8
Intra-arterial administration		
Epinephrine (0.01 mg.)	0.9	6.7
Dihydro ergot alkaloids (0.3 mg.)	2.3	1.5
Papaverine (30 mg.)	2.8	6.8
Tolazoline (25 mg.)	5.6	2.2
Nylidrin (5 mg.)	2.8	8.4

*Volume of blood flow in milliliters per 100 Gm. of tissue per minute.



Nylidrin

(Phenyl-2-butyl norsuprifen hydrochloride)

to lower blood cholesterol is unique.[126, 191] The drug is used most often in patients with cerebral arteriosclerosis, Ménière's syndrome, and vertigo due to impaired cerebral circulation.

Nylidrin. Nylidrin has unique vasodilating properties and differs from other vasodilators in chemical structure and pharmacologic action. It is effective orally, intravenously, intramuscularly, and intra-arterially. It is relatively safe and has low toxicity. Nylidrin is a catecholamine and acts as a vasodilator of peripheral muscles. The site of action, directly on vascular smooth muscle, is the same as that of other sympathomimetic amines. From an analysis of the over-all pharmacologic effects of a group of vasodilators of the amphetamine series, it appears that nylidrin combines the most desirable properties for a safe vasodilator with minimal toxicity, optimal tolerance, comparatively quick action, and long duration of effect.[54] The usual dose is 6 mg. three times per day orally or 5 mg. intramuscularly or intra-arterially.[5, 77]

Circulatory effects in skin and muscle. Nylidrin has only a slight vasodilator effect on the skin of fingers or toes and a greater effect on muscle vessels.[88, 192] Table II shows the relative effects on the muscle circulation of the calf as compared with the skin of the foot after the intra-arterial injection of 5 mg. of nylidrin. Intra-arterial nylidrin is more effective than tolazoline, papaverine, or the dihydro ergot alkaloids on muscle circulation. Vasodilatation is minimal in the skin of the foot.[170] Muscle clearance studies (Fig. 6) have shown a definite increase in the rate of clearance of radioactive substances from injected muscle, and this indicates improved nutritional circulation; plethysmographic studies of muscle show increased total blood flow (nutritional plus shunt flow).[192]

Cardiac output and blood pressure. Stroke volume and heart rate are moderately increased. Total peripheral resistance is decreased by an average of 23 per cent.[27] Cardiac minute volume measured by albumin I^{131} with a scintillation counter on the chest is increased. The pulsations of the left ventricular border shown with the x-ray kymograph are increased, and the height of the IJ waves of the ballistocardiogram are also increased.[190] The blood pressure shows characteristic changes, with a slight rise of systolic and fall of diastolic pressure. At times, the diastolic pressure falls rather dramatically.[152]

Adrenolytic and sympatholytic effects. These have not been demonstrated. At times, there have been decreased circulation of the skin and increased muscle blood flow, but these represent diversion of flow from skin to muscle[26, 99] and probably results from direct vasodilating action in muscle and not from adrenosympatholytic block.

Renal blood flow. This decreases slightly at the height of drug effect.[192]

Eye. The electroretinogram shows changes, and these are said to correlate with increased circulation to the retina.[103]

Ear. Circulatory disturbances of the inner ear, especially labyrinthine artery insufficiency characterized by tinnitus, deafness, and a disturbance of balance, have been improved, which suggests an increased circulation to this area.[158]

Brain. Increase of total circulation to the brain was confirmed by Eisenberg,[49] who demonstrated, in persons with cerebrovascular disease, 43 per cent increase of cerebral blood flow after oral administra-

tion for more than 14 days; when the drug was administered for a shorter time, the effect was inconsistent. The increased cerebral flow was associated with a decrease of cerebrovascular resistance and in some cases slight decline of mean arterial pressure.[192] These findings agree with radioactive clearance techniques in animals in which an increase in the rate of clearance of I^{131} from white and gray matter was demonstrated.[192]

Coronary circulation. Very little information is available. Prinzmetal[144] has suggested that the drug be used to decrease nocturnal angina.

Indications. Nylidrin has been used in patients with ischemia and edema of muscle, ischemic night cramps, and cerebral vascular insufficiency. Because of the subjective nature of the responses in patients with intermittent claudication, evaluation has been difficult.[141] It has also been used in patients with arteriosclerosis and thromboangiitis obliterans. While ischemic ulcers, frostbite, cold feet, and Raynaud's disease might be expected to respond poorly because they are disturbances of skin circulation, in our studies, the skin circulation was increased slightly. There is the possibility of diverting blood from the skin when using muscle vasodilators. Good vasodilatation will probably result from the combined use of nylidrin and a skin vasodilator such as azapetine or tolazoline.

Contraindications. The drug is contraindicated in patients with acute coronary thrombosis, hyperthyroid tachycardia, paroxysmal tachycardia, and severe angina because of increased stroke volume and pulse rate. Although it has been suggested for nocturnal angina, it should be used cautiously.

Isoxsuprine. Isoxsuprine, which resembles nylidrin, was synthesized by Moed and Van Dijk.[128] Isoxsuprine relaxes vascular smooth muscle[21] and uterine muscle. It is given in 10 mg. doses orally, intravenously, intramuscularly, or intra-arterially. When given intra-arterially, there is little systemic effect, presumably because of fixation in the tissues. Gastrointestinal upset is not common, but postural hypotension may occur. Intramuscular or intra-arterial injection increases muscle circulation although the cutaneous circulation to the fingers and toes increases by only a small amount.[101] Radioactive iodine clearance from muscle is also increased, as is limb flow measured plethysmographically.[101] Decrease in the femoral arteriovenous oxygen difference is explained by an increase in shunt flow.[104] Radioactive iodine muscle clearance increases less than total blood flow (plethysmographic), and this suggests an increase in flow through both shunt and capillary vessels. Numerous studies have shown that isoxsuprine decreases peripheral vascular resistance, increases blood flow in muscle, and simultaneously slightly increases flow through the skin of the fingers and toes. In man, renal plasma flow is not increased after 10 mg. of the drug intramuscularly.[105] The cerebral vascular circulation increases, and there is a mild increase in the mesentery and coronary beds in animals. When many vascular beds are dilated simultaneously, the total peripheral vascular resistance falls and, in the absence of any compensatory change in cardiac output, the arterial pressure falls; however, measurements of arterial pressure show that blood pressure is maintained almost unchanged after therapeutic doses. After large doses, there is a drop in diastolic and mean blood pressures and an increase in cardiac output[101]; the latter can be accounted for almost entirely by the change in pulse rate, since there is only a small change in stroke volume. Changes seen in the ballistocardiogram suggest a change in the force of the cardiac contraction and may reflect a direct influence of the drug on myocardial function. The blood pressure compensation can be explained in part by normal pressor reflexes and in part by a specific cardiac influence. Increase in cardiac output in patients with mitral stenosis could not be demonstrated after administration of isoxsuprine.[104] This may have been due to the valvular defect which limited the

Table III. *Certain vasoactive agents and the vascular beds in which they are active*

Vascular bed and metabolic state	*Blood flow*		
	Increased	*Insignificant change*	*Decreased*
Skin	Azapetine Tolazoline Dihydro ergot alkaloids	Nylidrin Isoxsuprine	Nylidrin* Isoxsuprine*
Muscle	Nylidrin Isoxsuprine		Tolazoline
Heart (cardiac output)	Nylidrin Isoxsuprine	Cyclandelate β-Pyridylcarbinol	Dihydro ergot alkaloids
Kidney	Azapetine† Phenoxybenzamine†		Nylidrin
Brain	Nylidrin Isoxsuprine Dihydro ergot alkaloids‡		
Coronary circulation	Nitroglycerin Pentaerythritol tetranitrate		
Splanchnic system	Nylidrin Tolazoline		Ganglion-blocking agents§
Retina	Nylidrin Tolazoline Dihydro ergot alkaloids		
Pulmonary system	Tolazoline‖ Ganglion-blocking agents‖		Dihydro ergot alkaloids
Ear	Nylidrin		
Metabolism	Nylidrin	Ganglion-blocking agents	

*Large doses intra-arterially in patients with arterial obstructions.

†If decreased renal flow is due to epinephrine.

‡If cerebrovascular resistance is high, as in hypertension.

§Large doses.

‖If pulmonary hypertension was present previously.

output; studies in animals, however, show that the minute and stroke volumes are increased.[21, 98] The drug exerts a direct dilator effect on the walls of blood vessels, and adrenergic block is not an important action.

The indications and contraindications are essentially the same as for nylidrin.

Discussion

It is apparent that vasodilators must be selected intelligently for the treatment of patients with peripheral vascular diseases so that vasodilatation will be produced in the area in which it is needed. Table III lists several drugs and the vascular beds in which they are active. The following therapeutic principles should be followed: Cutaneous vasodilators are used in Raynaud's disease and as an aid in healing skin ulcers. Muscle vasodilators are used for ischemic night cramps, muscle atrophy, and intermittent claudication. Renal vasodilators are used for renal vascular insufficiency, especially when the circulation is limited by epinephrine. Cerebral vasodilators are used for cerebral vascular insufficiency and are probably most effective if the cerebral circulation is controlled by epinephrine or if vascular tone is high, as

in hypertensive patients. Splanchnic vasodilators are used for mesenteric artery insufficiency as shown by postprandial abdominal angina. Retinal vasodilators should be tried in patients with retinal artery ischemia and in some patients with diabetes. Pulmonary vasodilators are used in patients with primary pulmonary hypertension and secondary pulmonary hypertension, for example intraventricular septal defect. Labyrinthine artery dilators can be used when signs of ischemia of this artery are present, as in certain disturbances in balance, tinnitus, and deafness.

Vasodilators should be selected carefully for their effects on skin and muscle. Table II shows the relative blood flow of skin and muscle after reactive hyperemia, exercise, sympathectomy, and reflex heating, compared with that after various drugs—epinephrine, nylidrin, papaverine, tolazoline, and the dihydro ergot alkaloids. It is apparent that reactive hyperemia is a potent dilator of both skin and muscle vessels and is more effective than most drugs or procedures (Table II and Fig. 5).

The choice of a drug for the treatment of peripheral vascular disease has become more difficult with the increased number of drugs and variety of sites of action available. It is therefore important in choosing a drug to understand the underlying physiologic principles which regulate the peripheral circulation. The most important yardstick for the efficacy of a drug is probably the subjective report of the patient, but objective measurements should also be used. However, in view of the impracticability of trying all the available drugs on all patients, the primary choice should be based on fundamental physiologic considerations.

Although it is customary to classify peripheral vascular diseases as organic (e.g., occlusive) or functional (e.g., hyperreactive spasm or vasoconstrictive), it is rare that any clinical entity belongs in either category exclusively, i.e., the lesions encountered in most patients represent combinations of organic and functional diseases. Theoretically, rational therapy for these two basic disorders is distinctly different: occluding disorders respond to procedures which bring the blood supply around the occluded area, e.g., the opening of collateral circulation or removal of the occlusion by surgical or possibly by enzymatic action; in contrast, treatment of functional circulatory insufficiency includes localized dilatation by the release of excessive vasoconstrictor tone or other appropriate means. Because of the association of the two types of disorders, it becomes almost impossible to choose with absolute certainty between these two approaches to treatment; however, in each patient, it is useful to find which of these factors is the more important. It is therefore necessary to analyze each case carefully to decide upon a specific course of treatment; here, objective methods of assessing the peripheral circulation are very useful.

One should remember the altered vascular reactivity of vessels which may occur in various disease states such as peripheral arteriosclerosis or pheochromocytoma, etc., and therefore careful clinical observation is required. After sympathectomy, for example, epinephrine sensitivity develops, and certain adrenolytic agents are of value for the long-term treatment of these patients. The possibility of diversion of blood from a diseased area should be borne in mind. Also, combined therapy is usually advisable for the treatment of peripheral vascular diseases, with use of those drugs which have different sites of action in order to produce additive effects. This approach can be most successful when used with full knowledge of the actions of the available drugs.

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Pharmacology and toxicology of trichloroethylene

A critical review of the world literature

A review of the world literature on trichloroethylene has revealed a general inadequacy in medical reports and the need for further studies if this compound is to remain in the medical armamentarium. Even studies on toxicology leave much to be desired. It is hoped that the extensive bibliography provided will permit future investigators to approach studies of trichloroethylene with a readily available background of work already accomplished.

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Although tried for various medical purposes, trichloroethylene is now used mainly in anesthesia. The drug, discovered in 1911, has anesthetic properties which have been exploited only since 1941. Unfortunately, the many publications since that time consist mostly of uncritical clinical impressions on which are based the statements found in the majority of textbooks. Acceptable pharmacologic data are scarce and vary according to the species studied and the experimental conditions.

The toxicology of trichloroethylene is likewise a controversial field because many authors have ignored the distinctions between traces in the atmosphere and dangerous exposure and between the pure and the industrial or contaminated product. There is little doubt that in industry as in anesthesia, trichloroethylene can be lethal or lead to severe damage; but this need not be so.

The aim of the present review is to criticize the literature and perhaps to stimulate pharmacologic studies in a largely unexplored field.

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Historical background

This drug was discovered in 1864 by Fischer[145]: in preparing tetrachlorethane, he found a second volatile substance and identified it as trichloroethylene. It was soon adopted by heavy industry in Germany and Great Britain and was subsequently extensively used during World War I as a degreaser for machinery and as a solvent for organic products.[227] It soon became evident that the product was toxic, and in 1915 Plessner[327] reported the first 4 cases of trigeminal analgesia. At Oppenheim's[307] suggestion, Plessner tried it in the treatment of trigeminal neuralgia. Some years later, both published enthusiastic reports, but the efficacy of trichloroethylene in tic douloureux was seriously challenged by Oljenick[306] and Glaser[169, 170] in 1928 and 1931, respectively. In the United States, the drug was tried during the same period with little success in treatment of

angina pectoris and migraine. In the meantime, its narcotic properties were discovered in 1911 by Lehman[260] of Germany, and in 1933, Jackson[232] succeeded in anesthetizing dogs. After Herzberg[205] had demonstrated the safety of the purified product, his co-worker Striker[398] anesthetized humans. Their work caught the attention of Waters, who studied trichloroethylene in animals but found undesirable effects on cardiac rhythm.[427] His conclusions influenced the report of the A.M.A. Council of Pharmacology and Chemistry (1936) which warned that ". . . the available evidence did not seem to justify its acceptance and further investigation should be done before it was accepted." Interest in the drug then declined in the United States. In 1939, the British Government asked a joint committee of the Medical Research Council and the Royal Society of Medicine to find an anesthetic which was nonexplosive, inexpensive, and safer than chloroform and which could be used in wartime. Two members of the committee, Hewer and Hadfield,[206] reviewed the literature and became interested in trichloroethylene.

Subsequently, Chalmers, a London chemist who had anesthetized himself with it, communicated with Hadfield. Hewer and Hadfield then used Chalmers' compound on patients at St. Bartholomew's Hospital and in 1941 reported their first 127 cases. Hewer was subsequently surprised to learn that since 1936 a highly purified product other than Chalmers' had been on the market, the now well-known Trilene.

In 1944, 3 years after the introduction of trichloroethylene, *Lancet* published a warning against possible cranial nerve injuries when the agent was used with soda lime in a rebreathing system to absorb carbon dioxide. At the same time, Humphrey and McClelland[222] reported several cases of cranial nerve palsy, some leading to death. By 1945, however, McClelland,[270] Firth,[144] and others had clarified the problem, and since then trichloroethylene has always been used without soda lime. An interesting point is that Lehman[260] and Ott[314] in 1911 and 1931, respectively, had already warned against the association of the two.

After World War II, the use of trichloroethylene rapidly spread to the Continent and throughout the Commonwealth. It regained favor in the United States, although it is not as popular as in Great Britain. According to Stephen,[392] this is due to the fact that the American anesthetist is "wedded" to the use of the circle carbon dioxide absorption system. He nevertheless admits that in 1958, 35,000 L. was used in this country.

Physical and chemical properties

Trichloroethylene is a colorless aliphatic carbohydrate, liquid at usual temperatures, with the fruity odor of chloroform but without its pungency. It is practically insoluble in water and mixes in all proportions with the usual organic solvents. It is inexpensively prepared by treating ethylene with chlorine to form tetrachlorethane, which reacts with lime slurry to give trichloroethylene:

$$C_2H_2 + 2\ Cl_2 \rightarrow C_2H_2Cl_4$$
$$2\ C_2H_2Cl_4 + Ca(OH)_2 \rightarrow$$
$$2\ C_2HCl_3 + CaCl_2 + 2\ H_2O$$

Under normal circumstances, trichloroethylene is not flammable in air, but mixtures from 10.3 to 64.5 per cent with pure oxygen or with air and oxygen concentration above 24.3 per cent are flammable if the temperature is above 25.5° C. The vapor ignites at 463° C. in air and at 419° C. in oxygen.[241] Two explosions[148, 160] were reported during the use of cautery for oral surgical operation in patients inhaling trichloroethylene, but the accident must probably be attributed to combustible gases generated in the alimentary tract.

Stability. In the presence of air and light, the compound decomposes, with formation of dichloracetylene, chlorine, hydrochloric acid, carbon monoxide, and phosgene[312] in amounts sufficient to injure

cranial nerves.[111] The decomposition is catalyzed by moisture, acids in rubber, resins, and metals, especially aluminum powder[312] but is retarded by storage in amber-colored bottles and addition of 0.01 per cent thymol blue. It also decomposes at temperatures above 125° C.,[397] hence the warning against its use in the presence of a cautery or open flame.[359] The danger, however, seems to be more theoretic than real, and in ordinary anesthetic practice, toxic concentrations of those decomposition products are never reached.[215]

Utilization in anesthesia. In 1934, TCE was accepted by the USP under the names trichloroethylene, trichlorethane, and trichloran. The USP specifies that it must contain no less than 99.5 per cent of pure product, that its thymol blue content, if any is used, be between 0.010 and 0.012 per cent, and that it must be sold with a warning against use with soda lime.

The authors who investigated the question were satisfied with the high standards of purity of the commercial product, especially of Trilene.[53, 211, 232, 308] The commercial product is checked for three groups of impurities: excess of acids, presence of chlorine, and presence of chloride ions.

Table I. *Physical characteristics of trichloroethylene*

Characteristic	*Data*
Molecular weight	131.4
Boiling range	87.14°–87.55° C.
Specific gravity	1.465 at 20.4° C.
Vapor density	4.53 at 25° C.
Absolute vapor pressure	60 mm. Hg at 20° C.
Melting point	83° C.
Latent heat vapor	58 calories per gram
Specific heat in liquid form	0.32 calories per milliliter or 0.22 calories per gram
Distribution coefficients of solubility:	
Water/air	3 at 20° C.; 1.6 at 37° C.
Blood/air	18-22 at 20° C.; 8-10 at 37° C.
Plasma/air	16-20 at 20° C.

Metabolism

Trichloracetic acid. A metabolite of trichloroethylene giving a positive Fujiwara reaction in urine was discovered in 1933[68] and isolated from the urine of dogs in 1938.[37] It proved to be trichloracetic acid by comparison with known salts. The product was discovered in human urine in 1945[335] and its presence confirmed after anesthesia,[149, 168] after exposure in factories,[2, 3, 126, 136, 137, 153, 178, 386] and after accidental ingestion.[421] It has also been found in rat,[2, 3] rabbit,[136, 137] and bovine[374] urine.

Most investigators report that trichloracetic acid appears first in blood and then in the urine within 3 to 4 hours after inhalation of trichloroethylene, in amounts proportional to the quantity of the latter absorbed. Elimination reaches a maximum on the second or third day and then decreases exponentially for 10 to 15 days.* [2, 31, 318, 335] In cases of oral ingestion, elimination of trichloracetic acid is even slower.[421] A few hypotheses have been advanced to explain the slow elimination: displacement of trichloracetic acid from proteins,[31, 384] linkage to red cells,[136, 137] or slow diffusion from some organ in which trichloroethylene is fixed and slowly metabolized.[335] With one exception,[382] all authors agree that free trichloracetic acid is not detectable in blood until a few hours after the end of trichloroethylene administration, but as soon as it appears in the blood, it can also be found in urine, in amounts proportional to blood concentration; the same mechanism occurs where sodium trichloracetate is injected intravenously.[2, 318]

Where does this metabolism take place? In spite of discrepancies in results, comparisons of trichloroethylene and trichloracetic acid concentrations in rodents and dogs point toward the lungs and possibly the spleen as centers of transformation.[87, 136, 137]

Various factors modify the rate of transformation.

*Z. Bardodej: Unpublished data.

Species. Trichloracetic acid is present in the following proportions after inhalation of trichloroethylene: in dogs, 5 to 8 per cent[37]; in rats, 4 per cent[150]; in rabbits, 0.5 per cent[2, 3]; in man, 6 to 16 per cent.[2, 3, 29, 178, 382, 386]

Duration and intensity of exposure. While some reports claim that high concentrations and prolonged exposures increase the rate of transformation,[150] others describe an opposite effert.[29]

Decrease. This occurs with increasing age, obesity, infection, postoperative complications, low urinary output, and low basal metabolic rate.[168, 178]

Diurnal changes. Daily variations have been reported.[386]

Drugs. Insulin and glucose[386] and pyrazolone antidiuretics increase the urinary concentration of trichloracetic acid, while after ingestion of disulfiram, trichloracetic acid disappears from the urine.[151]

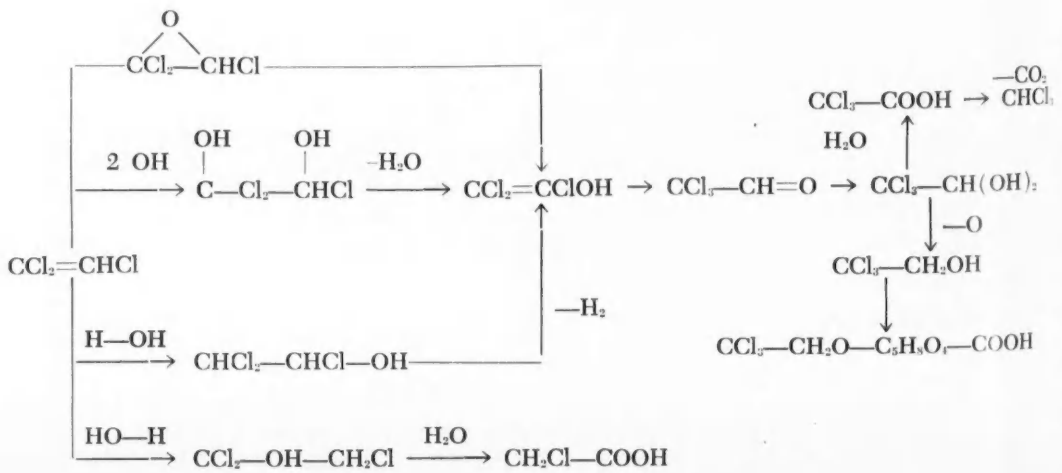
Another detail about trichloracetic acid concerns its utilization as a toxicologic test, first suggested in 1945.[335] Correlations between the symptoms of intoxication and urinary concentration of trichloracetic acid[2, 3, 126, 136, 137, 149, 178, 217] have been found, but this is not always the case.[24, 153] Differences in titration techniques can explain the discrepancies.[126] In spite of these objections, the concentration of trichloracetic acid in the urine as an index of exposure to trichloroethylene has gained popularity among industrial hygienists, who have based many tests on this principle.[2, 3, 37, 126, 132, 136, 137, 154, 424]

Trichlorethanol. Trichlorethanol was discovered conjugated with glucuronic acid in plasma and urine of dogs,[70] calves,[374] and man[29, 384, 386] in amounts from 0.5 to 7 times that of trichloracetic acid. All investigators report rapid elimination, although one group[386] has recorded an average elimination time of 350 hours in man.

Monochloracetic acid. Postulated in 1952,[241] monochloracetic acid was found in human urine in 1954.[384, 386] It represents 4 per cent of the trichloroethylene retained in the organism; its elimination starts a few minutes after onset of inhalation, reaches a maximum at the end of the exposure, then falls exponentially for an average of 112 hours.[384, 386]

Other products of metabolism. Intensive investigations have failed to reveal any other product and no evidence of transformation to chloroform.[29, 36]

Pathways. Since both trichloracetic acid and trichloroethylene are metabolites of chloral hydrate, the latter has been proposed as an intermediary product of transformation of trichloroethylene, but several investigators have failed to find it in the blood of humans and dogs.[31, 70, 71, 72] The transfer mechanism diagramed below has been suggested[31]:



Pharmacology

Cardiovascular system.

Blood pressure. So many factors can influence arterial blood pressure during anesthesia that many of the clinical impressions implicating the agent are valueless. While many authors find no change in blood pressure,[48, 63, 174, 179, 181, 206, 232, 276, 423] others report either an increase[45, 238] or a decrease.[195, 248, 267] Experiments on dogs suggest either no change[112] or, more often, a fall in pressure, possibly the result of splanchnic vasodilatation.[250, 429] There are no studies on cardiac output, peripheral resistance, or cerebral venous pressure.

Blood vessels. Trichloroethylene is supposed to cause less capillary oozing than ether,[128, 192, 206, 207, 209, 211, 212, 223, 228, 237, 323] except when tachypnea occurs.[311] In frogs, the compound causes moderate constriction of arterioles[250] and of the arteriolar side of capillaries.[279] The effects on coronary arteries in the dog are inconsistent,[250] or there may be no effects.[429] In rabbits and macaques, a marked increase in the cerebral blood flow is found.[301] None of these studies bears careful scrutiny.

Cardiac rhythm. Since arrhythmias are difficult to detect without electrocardiographic studies and many factors can influence cardiac rhythm besides the agent and anesthetic concentrations, it is not surprising to find contradictions.

In some reports, arrhythmias are nonexistent or rare (bradycardia, less often tachycardia, or extrasystoles), provided there is no overdosage.[11, 15, 61, 63, 131, 154, 179, 192, 194, 206, 208, 220, 248, 301, 311, 354, 368, 389, 415, 423] In others, trichloroethylene causes frequent and dangerous arrhythmias: auricular fibrillation and flutter, multifocal ventricular extrasystoles, pulsus trigeminus,[134, 166, 308, 426] and in a majority of cases bradycardia.[174, 176, 237]

Frequent ventricular extrasystoles increasing with airway obstruction were noticed after oral intoxication.[110] Upon correction of the obstruction, although the victims were tachypneic, the cardiac rhythm first returned to normal; then restoration of normal respiration occurred; this suggested a primary action of the heart. Procaine was the drug of choice in treating these arrhythmias.[110]

In 1943, an exceptionally good clinical study[33] revealed two common types of arrhythmia: (1) During induction, changes probably of vagal origin (bradycardia, atrioventricular block, and mainly atrioventricular nodal rhythm) occurred which disappeared when anesthesia was deepened. They have frequently been reported with other agents and were harmless and difficult to detect without recording an electrocardiogram. (2) In deeper planes of anesthesia, auricular or more often ventricular premature contractions were found. These also occur with chloroform and cyclopropane, in the former case probably a forerunner of ventricular fibrillation.

Pharmacologic studies of arrhythmias in animals are inconclusive. While two investigators[53, 427] found arrhythmias in dogs persisting as long as anesthesia lasted, another found no arrhythmias.[276] Rodents may develop arrhythmias during induction, but these quickly disappear.[53]

Arrhythmias and tachycardia have been reported in patients being anesthetized with trichloroethylene and receiving local applications of epinephrine,[33, 175, 265] although small amounts of a 1:200,000 solution are sometimes permitted.[88] After accidental ingestion of trichloroethylene, epinephrine increases arrhythmias and has proved fatal in some cases.[110]

In dogs anesthetized with trichloroethylene, injection of epinephrine causes atrioventricular block and ventricular extrasystoles occasionally followed by ventricular fibrillation or asystole.[57, 97, 110, 112, 291, 431] The minimal lethal dose was found to be 8 μg per kilogram.[291] Several drugs appear to protect against epinephrine-induced arrhythmias in dogs: (1) Dihydroergotamine[431] is postulated but not yet confirmed.[110] (2) Chlorpromazine[57] and perphenazine,[112] with several possible mechanisms, are suggested.[57] Hypotension thus induced, depression of the conducting

tissue, an adrenergic blocking action, or a direct hypothalamic depression may occur.

Cardiac arrest. Up to 1960, 26 cases of cardiac arrest with trichloroethylene had been reported, but the actual number is probably much higher. It is likely that factors other than the agent per se were to blame. Few reports include a decription of circumstances preceding the accident. Some reports implicate anoxia,[275] hypovolemic shock[396] overdosage,[124] aspiration of vomitus,[106] and overdosage of local anesthetics.[206] Several articles suggest primary arrest with light anesthesia in well-ventilated patients.[46, 106, 124, 130, 195, 300, 312, 396]

Respiration. Although tachypnea with trichloroethylene has been observed for a long time, its significance is still undetermined. Many consider it to be a sign of overdosage in man[13, 48, 61, 88, 98, 101, 116, 173, 174, 192, 195, 208, 211, 212, 220, 238, 288, 299, 311, 368, 389, 398, 423, 437] as well as in dogs,[291, 308, 427, 429] cats,[260] and rodents.[53, 404] Some report it during induction, either in premedicated or nonpremedicated patients,[128, 179, 237] especially when induction is started with trichloroethylene instead of another agent.[61, 63, 128, 179, 192, 208, 311] Here, too, tachypnea could be due to temporary overdosage during rapid induction. Shortly after the introduction of trichloroethylene in Great Britain, in order to decrease the incidence of tachypnea, many began induction with a thiobarbiturate.[63, 116, 131, 208, 238, 311] This may not only fail to decrease the incidence of tachypnea[174] but in some cases increase it.[168] Children, especially under the age of 2, seem prone to develop tachypnea,[15, 116, 389] but it is illogical to attribute it to a more sensitive respiratory center rather than to some features of pediatric anesthetic technique such as poor premedication or overdosage in an attempt to hasten a stressful induction.

Although overdosage is blamed in the majority of cases, some authors suggest that a few patients are sensitive to trichloroethylene and develop tachypnea as soon as they inhale the agent.[61, 88, 116, 131, 211, 212, 220, 229, 423] In these cases, reduction of the concentration and administration of a maximum amount of oxygen, then a change to another agent if these measures fail, are advised.

Treatment of tachypnea is suggested by the previous observations: avoidance of trichloroethylene in young children, slow induction after intravenous thiobarbiturates, and use of the least concentration compatible with anesthesia. Other measures suggested involve high concentration of oxygen[101, 231, 311, 423] and administration of 25 to 50 mg. of meperidine intravenously.[11, 88, 131, 239, 389, 390, 391] The mechanism of the effect of meperidine is still unknown. It may be a reduction in the concentration of trichloroethylene needed, or inhaled, a direct action upon the respiratory center,[116] or suppression of bronchospasm caused by trichlorothylene.[239]

Although several reports consider tachypnea to be harmless,[15, 415] it has been followed by cyanosis[398] and respiratory arrest[101, 179, 220, 237] and associated with bradycardia[174] or hypotension.[429] The danger of tachypnea is probably related to the severity, but this is rarely emphasized in the literature. Physiologic studies are rare and provide little information. Rate increases to 40 to 50 respirations per minute and minute volume increases concomitant with tidal volume decreases[116, 131] are described. Arterial oxygenation decreases by 25 per cent when the rate climbs from 20 to 40 per minute, but cyanosis does not occur as long as the respiratory rate remains below 60.[239] Arterial P_{CO_2} and pH in tachypneic patients remain normal.[301]

The tachypnea has been explained in various ways. By the mechanical[288] theory, the bases of the lungs fill with the heavy and relatively nonvolatile vapor of trichloroethylene, reducing the available lung capacity and leading to anoxic anoxemia. This has no experimental proof.

When trichloroethylene reaches a toxic blood level, it may cause histotoxic anoxia of the respiratory center and thus tachypnea.[101] This hypothesis is without experimental support.

Trichloroethylene may cause bronchospasm with retention of carbon dioxide, leading to tachypnea.[239] But if meperidine corrects this, morphine (a bronchoconstrictor) is also effective, while antihistamines are worthless and isoproterenol, epinephrine, amyl nitrite, and ether help in only a small proportion of cases.[116] It is therefore probable that meperidine acts through another mechanism,[116] depression either of the respiratory center or of the laryngeal, pharyngeal, or Hering-Breuer reflexes.

Experiments in cats[432, 433] suggest that the Hering-Breuer reflex involves not only afferent stretch receptors in the alveoli but also another group of receptors in small pulmonary vessels, causing a deflationary reflex. Comparisons of respiratory rate and volume with frequency and amplitude of discharges sent by receptors through isolated fibers of the vagus of decerebrate and spinal cats indicate that most agents increase excitability of stretch receptors and are thus largely responsible for the shallow respiration. Respiratory rate is affected differently. Deflationary reflexes which accelerate breathing are briefly stimulated, then paralyzed, by ether but are stimulated throughout by trichloroethylene. The tachypnea is thus probably due to the interruption of expiration as well as inspiration. The latter theory is the most attractive and widely accepted but is not above suspicion.[115] Many factors are ignored.[115, 116] ". . . The ability . . . to mobilize epinephrine is unknown so far . . . nor have the effects of extrapulmonary receptors been studied. Acid-base balance estimations have not been reported following its administration."[115]

Central nervous system.

Anesthesia. The anesthetic properties of trichloroethylene were first demonstrated in 1911[260] and rediscovered in 1934[232] and 1941.[206]

Induction is generally described as pleasant and rapid.[15, 45, 129, 140, 179, 181, 218, 220, 223, 237, 305, 323, 353, 360, 389, 415] A few authors describe excitement,[63, 174, 195, 208, 398] cough and laryngospasm,[11, 288] or slow and difficult induction.[61, 131, 280, 308] These contradictions are probably due to differences in technique and skill.

Although several workers claim to have reached plane 3 or 4 of the surgical stage and to have obtained good muscle relaxation,[179, 206, 308] the majority believe that because of cardiorespiratory complications, it is difficult and unwise to go deeper than plane 1 and that good muscle relaxation is difficult to obtain.[53, 88, 131, 174, 195, 210, 211, 212, 220, 223, 280, 311, 389, 423] However, for unknown reasons, relaxation of the mandibular muscles is often sufficient to permit oral intubation.[63, 129, 192]

Analgesia. The analgesic properties of trichloroethylene were first described in 1911,[260] confirmed when it was used for the treatment of painful syndromes,[166, 169, 243, 306, 351, 398] and re-emphasized in 1934 by Jackson[232] and by Hewer[206] in 1941. Hill,[218] in 1944, noticed the analgesia and retrograde amnesia, both occurring before the loss of consciousness. He was the first to use trichloroethylene for self-analgesia and built the first self-inhaler. Others after him who have reported their experience with self-inhalers emphasized analgesia and retrograde amnesia. A concentration of 0.5 per cent trichloroethylene vapor in air is sufficient to obtain analgesia.[48, 212] Analgesimetric investigations confirm the increase in pain threshold in conscious humans[200] and animals.[325]

Convulsions. Many factors can induce convulsions during anesthesia; however, reports on trichloroethylene rarely describe conditions existing at the time of occurrence. The convulsions reported begin with twitching of the face and are followed by generally clonic then tonic contractions of the limbs, extending to the whole body and accompanied or more often preceded by respiratory arrest and cyanosis. They generally cease with discontinuance of trichloroethylene and administration of oxygen.[91, 100, 101, 162, 173, 208, 266, 368, 389] Many of the reports of cases published occurred in young patients, and sensitivity in children has been postulated.[389]

Nervous sequelae of anesthesia. Postoperative sequelae reported were headaches[206, 308] and prolonged periods of drowsiness and mental aberrations.[118, 174, 223] The evidence suggests that they must not always be attributed to trichloroethylene alone. Acute psychosis has been reported after medical administration of pure trichloroethylene.[125, 349]

Addiction. Trichloroethylene is enticing because of its sweet smell and the elation it produces.[312] Many cases of addiction have been reported,[125, 242, 256, 304, 349, 400, 405, 442] especially in the feeble minded, in epileptics[304] or in confirmed drug addicts.[304, 349, 442] Trichloroethylene was popular among Dutch workers during World War II when it replaced their alcoholic beverages.[153]

Gastrointestinal system. Most authors report a minimal incidence of nausea and vomiting.[4, 15, 45, 61, 63, 74, 128, 192, 206, 208, 218, 220, 228, 248, 290, 311, 323, 333, 353, 360, 381, 389, 392, 406, 415, 423] Instances of frequent and serious vomiting have occurred.[118, 195, 223, 244]

Blood chemistry. Many factors besides the agent influence blood chemistry, but so far this point has not been emphasized in clinical surveys, and their value is therefore limited.

While some investigators report no change in blood sugar, even in diabetics,[63, 206] others claim that slight hyperglycemia during anesthesia[195, 301] and acetonuria are frequently found after trichloroethylene anesthesia.[195, 201, 208, 210, 211, 212]

One study reports no change in blood urea in 5 patients.[206]

Blood P_{CO_2} and pH remain unchanged in anesthetized humans.[301]

Uterine muscle. Satisfactory pharmacologic data are rare in the abundant literature concerning trichloroethylene and its use in labor. The strength of uterine contraction is difficult to measure, and the physician has to rely on subjective notions such as pain relief, etc. Though most investigators report no uterine relaxation,[107, 154, 216, 229, 320, 354, 372, 380] a few claim a decrease in strength[74] or frequency[48] of contractions or slowing of labor.[127, 197] A study of uterine contractions through recording amniotic fluid pressure fluctuations suggests that trichloroethylene improves the spasm of the lower segment and hypertonic inertia but is less effective in hypotonic uterine contractions, and prolonged administration weakens contractions.[263]

Isolated muscle strips of gravid and nongravid human uterus show no decrease in tone or strength of contractions after 4 minutes of trichloroethylene, while most other anesthetics are marked depressants.[401] This probably relates to the potency of the anesthetics and the depth of anesthesia produced. After trichloroethylene inhalation, the strength of contractions of human fallopian tubes decreases by 10 per cent but remains normal in type, amplitude, and frequency.[425]

The fetus. Most obstetricians consider trichloroethylene harmless to the baby, unless gross overdosage occurs.[14, 102, 155, 176, 197, 216, 290, 301, 354, 376, 379] Some claim quicker onset of respiration at birth[74] and lower neonatal mortality.[368] Disadvantages do exist, however, such as fetal bradycardia[48, 320, 354] or depressed respiration after prolonged administration.[368]

In sheep, the drug quickly reaches the fetal circulation, where its concentration becomes higher than that in maternal blood.[200] The reason for this phenomenon is unknown, but carriage by erythrocytes does not seem to be a factor.[200]

In humans, oximetry reveals no measurable change of blood oxygen saturation in full-term babies whose mothers receive trichloroethylene.[403]

Toxicology

The problem of toxicity of trichloroethylene is complex for several reasons. The industrial product is far from being pure: (1) There have been wide variations in purity and manufacture at different times in different countries.[53, 304, 308, 323, 371, 389, 398, 404] (2) Even originally pure trichloroethylene decomposes easily into highly toxic products. Therefore the accidents are

bound to happen in industrial plants with poor hygienic conditions.

The extent of toxicity is a function of concentration of trichloroethylene vapor in the atmosphere. Many publications, however, do not indicate concentrations present at the time of the accident.

Two factors are of paramount importance: the actual duration and mode of exposure and the individual resistance. Both are difficult to ascertain in an extensive study on toxicology.

In industrial toxicology, it is, of course, impossible to study subjects pathologically at the end of the exposure. The toxicologist therefore possesses little evidence on pathologic changes and has to rely on subjective neurologic symptoms which are difficult to measure and not always related to the concentration of trichloroethylene inhaled.[24, 153] Symptoms may be due to other degenerative diseases, not infrequent among older workers, exaggerated by malignancy, or denied because of euphoria, which is often part of the syndrome.

There are no clear-cut criteria for distinguishing between acute and chronic intoxication, especially in human toxicology.

In the ensuing discussion, a sharp distinction will be made between the effects of industrial (unpurified) and of medical (pure) trichloroethylene. Little attention will be paid to early animal experiments in which a grossly contaminated product was used and which produced major liver and kidney damage in dogs,[39, 257] rabbits,[81] and guinea pigs.[79, 260, 287]

Industrial toxicology.

Acute exposure. Dermatitis and eczema as well as first, second, and third degree burns[21, 31, 269, 277, 405] or conjunctivitis[5, 31, 422] can occur after contact with liquid trichloroethylene or with concentrated fumes.[366, 400, 422]

Sudden death has been described upon exertion shortly after intense exposure. Since autopsies were unrevealing, ventricular fibrillation has been suggested as the cause.[10, 202, 246]

Several reports suggest that fatalities are always due to contaminants[66, 146, 419]; however, even recent reports often fail to mention any search for unknown toxic products.

Cases of accidental ingestion present a uniform picture.[51, 110, 153, 246, 255, 295, 304, 393, 405, 408] Shortly after ingestion, the victims develop inebriety, vomiting, and diarrhea and, if the dose has been large, lapse into coma followed either by death (pulmonary edema and liver and kidney necrosis at autopsy) or by recovery with transient neurologic sequelae (amnesia, headache, numbness and weakness of extremities, psychosis, or hemiparesis).[51]

Acute industrial exposure by inhalation also leads to severe symptoms: the patients rapidly pass into coma; they die as a result of liver and kidney failure[78, 167, 187, 188, 282] or recover, either without sequelae[188, 324] or more often with liver and kidney lesions,[66, 412] nerve damage, cranial nerve palsies,[352] inebriety,[1, 31] headaches, and psychic disturbances.[240]

Chronic exposure. When good hygienic conditions exist, contact with trichloroethylene does not necessarily imply dangerous exposure, which explains why some report few symptoms[1, 66, 153] while others record severe accidents and death.[419] The symptoms of chronic exposure are chiefly neurologic: (1) Psychic disturbances include neuroses, restlessness, fatigue, anorexia, euphoria, and irritability.[2, 31, 178, 183, 254, 269, 400, 422] (2) Autonomic dysfunctions are hot flushes, perspiration, gastrointestinal disturbances, dermographism, fainting spells, and cardiac irregularities.[1, 31, 166, 178, 400] (3) Transitory lesions of the cranial nerves,[166, 253] especially trigeminal palsy,[328, 329, 400] or lesions of the optic nerve, involve optic nerve atrophy and retrobulbar neuritis.[18, 153, 178, 253, 328, 329, 400] (4) Disseminated neuritis and polyneuritis with muscle paralysis and loss of sensation are found.[54, 178, 253, 254, 269] (5) Present may be cerebellar syndromes such as tremor, ataxia, and vertigo.[2, 5, 8, 31, 178, 183, 254, 319, 400, 422]

Nonneurologic symptoms are reported: (1) Dyspnea and angina pectoris may be

found.[2, 31, 54, 166, 178, 422] (2) Intolerance to alcohol[2, 31, 254, 319] similar to that produced by disulfiram[54] can occur, which suggests aldehyde accumulation and interference with the metabolism of acetylcholine.[54] Diminution in the rate of oxidation of alcohol is also possible.[54] (3) Toxic effects have not been observed in the kidneys, and liver damage is denied by some[183, 400] but assumed by others who found abnormal results of liver function tests.[254, 269] An increase of total blood lipids and of certain of their fractions has been reported.[183] (4) The changes described in the morphologic state of the blood are so insignificant and so frequently met in a normal population that it is difficult to draw any conclusions. After acute intoxication, either no change[180] or more often moderate and transient leukocytosis or polycythemia may be present.[78, 96, 183, 317, 411] In one group of investigations on chronic exposure, either no changes were reported[193] or else infrequent mild anemia and leukopenia,[32, 56, 104, 183, 402] while another group found moderate anemia and leukopenia in the majority of those exposed.[183] Intoxicated subjects with other symptoms often show mild anemia, sometimes after transitory polycythemia and leukocytosis.[17, 103, 120, 138, 139, 303, 400, 410, 411]

Several measures have been proposed to minimize the dangers of industrial intoxication[31]: dismissal of workers with neurologic and psychic disturbances and alcoholics; avoidance of direct contact (use of gloves, masks, goggles); exercise in open air and a diet rich in proteins and vitamins B and C; detection of overdosage (biologic tests and atmospheric controls); and lowering of maximum allowed concentration (MAC). Thus the present MAC admitted in the United States is 200 parts per million (p.p.m.), a value far above the 5 to 50 p.p.m. recommended by authorities.[2, 3, 31, 126, 153, 178] The only countries where these levels are mandatory are Sweden (30 p.p.m.), U.S.S.R. (10), and Czekoslovakia (9). Great Britain allows 400 p.p.m., Italy 100, and Switzerland 150.

Medical toxicology. Although two German chemists[260, 314-316] had described its instability in the presence of soda lime, trichloroethylene was administered frequently with carbon dioxide absorbents until 1943, when several British journals reported strange accidents.[76, 122, 131, 173, 222, 268] A few hours after the procedure, the affected patient would develop headaches and vomiting, then anesthesia, paresthesia, and palsy in the trigeminal area, followed by facial herpes. Several patients died with a syndrome of encephalitis confirmed by autopsy.[122] In each case, trichloroethylene had been used with soda lime during the procedure or shortly before. The absorbent was suspected, and the previous studies were confirmed.[222] At temperatures over 130° C. in the presence of KOH or NaOH, trichloroethylene decomposes into dichloracetylene and NaCl:

$$C_2HCl_3 + NaOH \rightarrow \underset{\underset{C—Cl}{|||}}{C—Cl} + NaCl + H_2O.$$

Dichloracetylene is highly toxic to rodents,[222-224] in which it produces a lethal encephalitis.

British investigators later found that the decomposition of dichloracetylene occurs as follows:

In the presence of oxygen, generating phosgene:

$$\underset{\underset{C—Cl}{|||}}{C—Cl} + O_2 \rightarrow OCCl_2 + CO + (?)CO_2.$$

In the presence of H_2O, generating several products which are then hydrolyzed into acids:

$$\underset{\underset{C—Cl}{|||}}{C—Cl} + H_2O + O_2 \rightarrow \underset{\diagdown\,O\,\diagup}{CHCl \quad CCl} + CH_2Cl_2 + COCl_2$$

All these chemicals are highly toxic. Several factors condition the production of dichloracetylene[135, 144]: (1) In a humid atmosphere, dichloracetylene is quickly hydrolyzed. (2) Temperature is of paramount importance. No dichloracetylene appears below 45° C.; above 45° C., trichloroethylene decomposes proportionally to

the temperature. (3) Decomposition is proportional to the alkalinity of soda lime. (4) The decomposition of trichloroethylene is inversely proportional to the size of the granules of soda lime and the rapidity of passage of trichloroethylene over them. The reaction is strongly inhibited by addition of 10 per cent silica to the lime. Very little dichloracetylene appears in the presence of ether, which probably fixes the dichloracetylene then releases it slowly.

Trichloroethylene has not purposefully been used in circle absorbing systems since 1944, but accidents still occur in parturient women given trichloroethylene throughout labor and subsequently anesthetized with absorption systems.[312] Experiments suggest that in animals given trichloroethylene and then allowed to breathe room air for 15 minutes, the concentration of halogens in the lungs is low enough to permit the use of soda lime.[135] In man, however, maintenance of a nonrebreathing system in those cases is advised.[234]

Skin. Macular[308] and maculopapular[173] rashes and lymphedema[237] have been noticed at induction of anesthesia. Flushing of the face has also been reported.[232, 299] Changes in skin temperature have not been found during inhalation.[267]

Nervous system. There are no histologic descriptions of anesthetic complications in man.

Dogs,[19, 20] after a large intravenous dose, generally convulse, lapse into coma, and die, but the autopsy may be negative; after repeated smaller injections, dogs develop transient tremor and ataxia; the autopsy reveals degenerative changes in the Purkinje cells of the cerebellum; after repeated minimal injections, total destruction of the several layers of cerebellar cells, mild degeneration of cerebral neurones, and swelling of myelin appear in dogs.

Kidney. Postoperative urinalysis suggests no renal damage,[63, 206] and this is confirmed by animal investigations: neither dogs,[302, 308, 371] rats,[302, 404] nor rabbits[301] show histologic changes or pathologic conditions on renal tests after subacute and chronic exposure. Toxic nephritis has, however, been described in rodents after acute exposure.[53]

Liver. Fatal hepatic failure has been reported following anesthesia; the autopsy revealed generalized acute necrosis.[16, 44, 113, 122, 198, 203, 320] Most of these patients, however, had complicating diseases such as malnutrition,[113, 120] toxemias,[44, 113, 198] and burns or had received transfusions.[16, 203, 439] The common liver function test results after anesthesia are unchanged[168] or moderately and transiently[9] disturbed. In dogs, acute exposure yields a normal sulfobromophthalein retention test[347] and a normal[235] or slightly altered[205] histologic picture, while subacute exposure causes marked sulfobromophthalein retention[347] or more pronounced, but transient, histologic changes.[302, 308, 371] After chronic intoxication in rats, authors have reported normal histologic[404] and liver test results,[302] although some suspect a moderate toxicity as shown by prolonged sleeping time with barbiturates[326] or histologic pictures of venous congestion and fatty infiltration.[53]

Blood elements. With the exception of one report of anemia in dogs,[371] subacute and chronic toxicity studies in dogs and rodents reveal no changes in the blood picture.[235, 302, 331] Aplastic anemias in cattle fed soybean the oil of which has been extracted with trichloroethylene (TCESOM) have been known since 1917.[337, 395] Fatal depression of the bone marrow can be produced experimentally in cattle by feeding TCESOM,[338] while trichloroethylene itself[338] and the products of its autooxidation[374] are harmless. Recent investigations demonstrated that the harmful agent was present in the protein fraction[272] and later[273] that trichloroethylene heated with cystein and –SH groups would form S–(transdichlorovinyl)-L-cysteine, a substance highly toxic to the bone marrow of calves and rodents.[273] Toxicity in man has not been established, although some investigators working with this product have developed dermatitis and swelling of the mucosas.[272, 273] The compound has been tried on patients with leukemia, polycythe-

mia, and metastases, but with indeterminate results.[357] The flesh of cattle thus intoxicated seems harmless when fed to other bovines and is probably harmless to man.[344]

Other systems. After acute or chronic exposure, dogs revealed no irritation of the respiratory tract[32, 205, 235] or histologic changes in spleen, adrenal glands, heart, and striated muscles.[205, 302]

Some workers found no changes in lungs and other viscera in rats,[302] while others reported collapsed alveoli[404] or even consolidation, hemorrhage, emphysema,[53] and cloudy swelling of the myocardium.[53] Growth is unaltered.[302, 404] In rabbits, neither viscera nor growth was affected by chronic exposure.[302]

Medical applications

Anesthesia.

General surgery. Although trichloroethylene has been given for most procedures, from tonsillectomy to gastrectomy,[33, 101, 131, 179, 427] a review of the literature suggests that it is frowned upon for some operations: (1) intrathoracic surgery, probably because of the tachypnea and the difficulty in controlling respiration in a nonrebreathing system[11, 280]; (2) pediatric surgery, where it frequently causes an uncontrollable tachypnea[11, 311, 388]; and (3) abdominal procedures, in which, after some early enthusiasm,[207, 310] it has fallen into discredit.[11]

Trichloroethylene is often recommended for procedures with which little relaxation is needed: in orthopedics,[64, 206, 237, 415] in plastic surgery,[174, 323] in ophthalmology,[208, 423] for thyroidectomy,[212, 311] and in operations on the ear, nose, and throat.[22, 86, 228] For minor procedures, either for complete anesthesia[45, 398] or for analgesia only, it may be used in urologic[320, 329, 332, 333, 407] ophthalmologic, ear, nose, and throat,[140, 142, 285, 305] and gynecologic[378] operations; aortography,[258] orthopedic manipulations,[320, 358] gastroscopy or esophagoscopy,[285] needle puncture in children,[406] and emergency room procedures[34, 64, 218, 244, 301, 320, 323, 358, 423] may be carried out with trichloroethylene. Numerous inhalers have been devised for these purposes: the Hill,[218] Freedman,[154] Calvert,[174] Trillite,[196] Columbus, von Hoseman,[48, 198] and especially the Cyprane and the Duke.[390]

Dentistry. Many procedures have been performed in dentistry, either by inhalation,[245, 334] with self-inhalers,[114, 127, 218, 233, 359, 363, 364, 436] or under complete anesthesia in which trichloroethylene is generally added to nitrous oxide.[12, 41, 42, 43, 49, 65, 80, 84, 161, 232, 244, 294, 365]

Obstetrics. Since 1943, trichloroethylene has been widely used in obstetrics either as an anesthetic[4, 64, 123, 216, 289, 293, 334, 376] or more generally as an analgesic administered through a self-inhaler[14, 34, 48, 64, 73, 74, 99, 102, 106, 129, 147, 154, 177, 182, 197, 198, 283, 299, 320, 373, 381] or through special obstetric inhalers (the Tecota,[213] Emotril,[210] Minnit,[210] McGuill,[10] and Finnie[143]). Trichloroethylene has enjoyed wide popularity in England, and obstetricians have not hesitated to administer it to cardiac[74, 320] and toxemic parturients[74, 154, 399] or for operative obstetric procedures.[4, 289, 290, 299] Objections, some debatable, have been raised: arrythmias and tachypnea,[216, 238] increased bleeding[216, 238] and hepatic failure in eclamptic patients.[44, 48, 198, 372] In 1949, the Royal Committee of Obstetrics and Gynecology of Great Britain[354] published the results of a survey: "... Although, well administered, the agent is safe for both mother and child, overdosage can occur and cause serious accidents." The Committee therefore prohibited its use by midwives but revised its opinion in 1957. Trichloroethylene has also been used for cesarean sections,[264, 399] although it was said to increase the maternal mortality.[394]

Other medical uses. From 1915 to 1930, trichloroethylene was tried in the treatment of trigeminal neuralgia, but enthusiastic reports[47, 172, 306, 307, 327, 328, 329] were not shared in the United States,[170] and it has been rarely used since. There was even less success in the treatment of migraine[164, 355, 356] and angina pectoris.[250, 267, 438] No serious clinical trials were made,

and it is probable that the vague beneficial effects were due to the narcotic properties.

Trichloroethylene has been used with some success in narcoanalysis[304, 343] and for the pain of terminal cancer patients, either by inhalation[111] or rectal administration.[350] It was also used in Great Britain around 1936 to clean wounds and burns[406] but not as a disinfectant, since it is bactericidal only in aqueous and phenolic emulsions.[350] It was at that time that trichloroethylene was purified and marketed.

Trichloroethylene has also been used as an anesthetic in veterinary surgery.[312]

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Pharmacologic effects of intravenous vanillic acid diethylamide in man

Vanillic acid diethylamide, a respiratory stimulant, was injected intravenously in doses of 0.5 to 2 mg. per kilogram. Effects were noted within 30 seconds; they lasted approximately 10 minutes. There was an average increase in tidal respiratory volume of 48 per cent and in respiratory rate of 24 per cent. Electroencephalograms were made before and after administration. The drug led to diminution of alpha activity, scattered high voltage spikes, cerebral dysrhythmias, and in 1 patient a tonic seizure. There were no significant changes in pulse rate or blood pressure.

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Vanillic acid diethylamide was found to stimulate the vasomotor center and exert an arousal effect, as well as to be a potent respiratory stimulant. When given intravenously[1, 3] to mice, it caused a marked increase in both frequency and amplitude of respiration and a moderate increase in arterial pressure. After an immediate, transient hypotensive effect, the diastolic pressure in animals with anesthesia hypotension was raised to nearly normal. The drug has been used in Europe as a respiratory stimulant in children and the newborn.[8, 9]

This article describes the acute effects of vanillic acid diethylamide, given intravenously, upon the respiratory system, cardiovascular system, and cerebral cortex in man and notes as well the presence, degree, and severity of undesirable effects in 9 men and 11 women ranging in age from 30 to 70 years. None had symptoms of pulmonary disease.

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Method

The subjects, who were hospitalized, were interviewed to develop rapport and cooperation. To decrease the physiologic and electroencephalographic variations from stress, it was explained that during an intravenous infusion they were going to have a special test. An intravenous infusion of 5 per cent glucose in water was first given. The subjects were instructed to lean back, breathe normally, close the eyes, and relax. The respiratory rate, resting tidal volume, pulse, and blood pressure were recorded over a control period of 10 minutes. Vanillic acid diethylamide was then injected into the infusion tube over a period of approximately 10 to 30 seconds in doses ranging from 0.5 to 2 mg. per kilo-

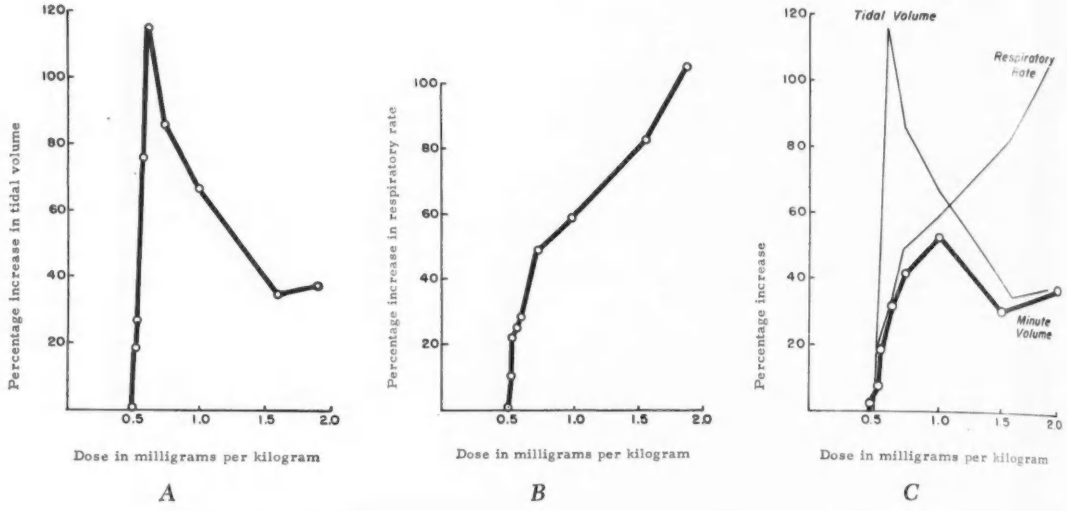

Fig. 1. Response to vanillic acid diethylamide. *A*, Effect on tidal volume at increasing dose levels in mean values. *B*, Increase in respiratory rate at increasing dose levels in mean values. *C*, Changes in minute volume superimposed on tidal volume and respiratory rate curves.

gram of body weight. The electroencephalogram was monitored in 10 of the patients.

Results

At the 0.5 mg. per kilogram dosage level, there was usually little or no effect. With progressively larger doses, the first respiratory change noted was an increase in tidal volume (Fig. 1, *A*). This was followed by an increase in respiratory rate (Fig. 1, *B*). While the respiratory rate was increasing, there continued to be an increase in tidal volume. When the minute volume was calculated, it appeared to increase rapidly to a maximum at a dosage level of 1 mg. per kilogram and then remained relatively constant (Fig. 1, *C*).

There were 4 patients in whom no response was noted with an intravenous dose of 0.5 mg. per kilogram. One, who had no response after 0.5 mg. per kilogram dose, had a 160 per cent increase in minute volume when the dose was increased to 0.62 mg. per kilogram. Another subject who had no response to the 0.5 mg. per kilogram dose had a 300 per cent increase in tidal volume after 0.72 mg. per kilogram.

One patient in the study had a tonic seizure; this lasted for 10 minutes and was associated with a 165 per cent increase in minute volume. It occurred at after 2 mg. per kilogram. Following the seizure, the patient was awake and alert, with no postictal confusion. Other effects were also noted: generalized pruritus lasting 3.5 minutes, a slight feeling of apprehension lasting 3 to 7 minutes, moaning noises, increased psychomotor activity lasting 4 to 10 minutes, and visual hallucinations of momentary duration; the latter were manifested by visions of colored, flashing lights. These effects may be the result of central nervous system stimulation.

No changes in either cardiac rate or blood pressure were observed in any of the patients after the infusion of vanillic acid diethylamide. Although there was an increased sense of well-being that persisted for up to 24 hours, no other latent effects were noted.

Twelve electroencephalograms were made on the first 10 subjects, all of whom had normal control electroencephalograms with a well-developed alpha rhythm, indicating a resting awake state. In all of the patients receiving respiratory stimulating doses of vanillic acid diethylamide, electro-

encephalographic changes developed simultaneously. There was a marked reduction in the amplitude of the alpha rhythm and a marked increase in the rate of the basic rhythm, suggesting an arousal effect. The subjects who received doses which did not produce a demonstrable effect on respiration had no appreciable change in the electroencephalogram.

Discussion

Vanillic acid diethylamide appears to be a potent respiratory stimulant which increases the frequency as well as the amplitude of respiration. The effects are dose related. The optimal dosage range for respiratory stimulation was approximately 0.75 to 1.5 mg. per kilogram. This may be contrasted with respiratory stimulation obtained with caffeine, which increases the rate of respiration but tends to decrease tidal volume. Unlike the situation with picrotoxin, there appears to be a considerable margin of safety between a dose that produces the undesirable effects of convulsions and the dose that stimulates respiration.[2, 4, 6, 10]

The most significant effect of vanillic acid diethylamide is the increase in tidal volume. Tidal volume increases until limited by the rate increase.

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Effect of steroids on bundle branch block caused by arteriosclerotic heart disease

A 5 day course of triamcinolone, 32 mg. daily, was given to 12 patients with coronary heart disease and an intraventricular conduction time of 12 seconds or more. In none of the cases was the duration of the QRS complex shortened by the steroid therapy.

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It has been reported that steroids may be beneficial in the treatment of complete heart block.[1-4, 7] The efficacy of steroids in this respect is dependent on more than their antiphlogistic action, for they accelerate atrioventricular conduction even in normal people.[5] It was therefore deemed of interest to determine whether steroids have a similar therapeutic action on bundle branch block.

Twelve male and female patients, ages 45 to 81, were studied on the medical wards. Patients were selected if the duration of the QRS complexes in the standard limb leads was 0.12 second or greater. All of the patients had coronary heart disease, and presumably the conduction defect was on this basis. Those with diabetes, severe congestive heart failure, acute infection, psychosis, tuberculosis, or peptic ulcer were excluded because of the danger of exaggerating the disease with steroids. The duration of the conduction defect was known to be 3 weeks in 1 case, over a year in 3 others, and indeterminate in the remainder. Each of the 12 patients was given 8 mg. of triamcinolone* four times a day orally for 5 days. Serial electrocardiograms were made a week before, during, and for a week after the course of steroid therapy.

In none of the 12 patients studied was there any change in the duration of the QRS complex. This negative result was of particular interest because of the recent report of a patient with left bundle branch block who did favorably respond to steroids.[6] In this case, the bundle branch block was present for at least 7 months, apparently because of a collagen disease, and yet a course of steroid therapy promptly resulted in the return of a normal intraventricular conduction time and its maintenance after the steroids were stopped. Perhaps, then, in those cases in which the intraventricular conduction defect is primarily due to inflammation, a trial of steroid therapy may be indicated.

We wish to express our thanks to E. R. Squibb & Sons for supplying the triamcinolone administered.

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*Kenacort.

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New information on drugs

Excerpts from the *Federal Register*

Regulations for Enforcement of the Federal Insecticide, Fungicide, and Rodenticide Act

Economic poisons highly toxic to man.

If the Secretary finds, after opportunity for hearing, that available data on human experience with any economic poison indicate a toxicity greater than that indicated from the . . . described tests on animals, the human data shall take precedence and, if he finds that the protection of the public health so requires, the Secretary shall declare such an economic poison to be highly toxic to man for the purposes of this Act and the regulations thereunder.

Terms defined and construed.

Economic poison. "Economic poison" includes insecticides, fungicides, rodenticides, herbicides, nematocides, plant regulators, defoliants, and desiccants. A product shall be deemed to be an economic poison regardless of whether intended for use as packaged or after dilution or mixture with other substances, such as carriers or baits. Products intended only for use after further processing or manufacturing, such as grinding to dust form or more extensive operations, shall not be deemed to be economic poisons. Substances which have recognized commercial uses other than uses as economic poisons shall not be deemed to be economic poisons unless such substances are (1) specially prepared for use as economic poisons, or (2) labeled, represented, or intended for use as economic poisons, or (3) marketed in channels of trade where they will presumably be purchased as economic poisons.

Nematocide. "Nematocide" includes only those products intended for preventing, destroying, repelling, or mitigating nematodes inhabiting soil, water, plants, or plant parts. The term does not include products intended for use against nematodes in or on living man or other animals.

Plant regulator. "Plant regulator" includes those substances intended to alter the behavior of ornamental or crop plants or the produce thereof through physiological rather than physical action. The term includes, but is not limited to, substances intended to accelerate or retard the rate of growth or maturation of ornamental or crop plants, enhance fruit set, prevent fruit drop, accelerate root formation and elongation, prolong or break dormancy of orna-

From vol. 26, 1961.

mental or crop plants or the produce thereof, but shall not include substances intended solely for use as plant nutrients or fertilizers.

Herbicide. "Herbicide" means any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any weed, including any alga or other aquatic weed.

Federal Hazardous Substances Labeling Act Relating to Specific Substances

Suspension of effective date of certain provisions.

A "highly toxic" substance may not always be defined in terms of animal tests, and a substance may be highly toxic because of human experience even though it will not meet the animal test definition. Examples of substances that have shown themselves to be highly toxic and hazardous by human experience are methyl alcohol and carbon tetrachloride. Such substances that have, by human experience, been demonstrated to cause serious injuries shall be considered "highly toxic" even though not meeting the test prescribed in section 2(h)(1) of the act, and shall bear the labeling specified in section 2(p)(1) for highly toxic substances.

Fat Preservative, Fat Antioxidant

Definition and standard identity.

Notice is given that the Commissioner of Food and Drugs proposes to establish a definition and standard of identity for the food fat preservative, fat antioxidant.

The proposed definition and standard of identity is as follows:

§55.1 **Fat preservative, fat antioxidant; definition and standard of identity; label statement of optional ingredients.**

(a) Fat preservative, fat antioxidant, is the class of food added to fats or to foods containing fats for chelating, sequestering, or combining action, and which serves to retard rancidity.

(b) The food is prepared from one or more of the following optional ingredients, and may appear in the combinations specified:

(1) Butylated hydroxytoluene.
(2) Butylated hydroxyanisole.
(3) Gum guaiac.
(4) Nordihydroguaiaretic acid.
(5) Propyl gallate.
(6) Tocopherols.
(7) Isopropyl citrate.
(8) Stearyl citrate.
(9) Citric acid.
(10) Monoisopropyl citrate.
(11) Ethylenediamine tetraacetic acid or its calcium and/or sodium salts.
(12) Glycerol monocleate monocitrate.
(13) Phosphoric acid.
(14) Combinations of two or more of the antioxidants listed in subparagraphs (1), (2), (4), and (5) of this paragraph.
(15) Combinations of citric acid, monoisopropyl citrate, and phosphoric acid, either alone or in combination with the antioxidants listed in subparagraphs (1), (2), (4), (5), and (14) of this paragraph.

(c) The name of the food is "fat preservative" or "fat antioxidant," or in lieu thereof the name "fat preservative ------" or "fat antioxidant ----------," the blank being filled in with the name or names of the optional ingredients used, as listed in paragraph (b) of this section.

(d) The label shall bear the name or names of the optional ingredients present in the article, as specified in paragraph (b) of this section, unless the nomenclature authorized by paragraph (c) of this section is used. In addition, the label shall bear adequate directions for use to insure that when used singly or in combination in fats or fatty foods the amount present will not exceed any tolerance limitation set by the regulations prescribed under the food additives amendment of the Federal Food, Drug, and Cosmetic Act (Part 121 of this chapter).

(e) Except for a fat preservative, fat antioxidant mixture sold as such, when a fat preservative, fat antioxidant, is present in a fabricated food as an ingredient, it may be declared as such without reference to the name or names of the optional ingredients present in the fat preservative, fat antioxidant.

(f) The labeling requirements of section 403(k) of the Federal Food, Drug, and Cosmetic Act shall be considered met if any fabricated food containing a fat preservative is labeled "fat preservative added" or "fat antioxidant added to retard rancidity."

Dated: January 19, 1961.

GEORGE P. LARRICK,
Commissioner of Food and Drugs.

Book reviews

Chemobiodynamics and Drug Design, by F. W. Schueler. New York, 1960, McGraw-Hill Book Co., Inc. 638 pages. $19.50.

It may safely be predicted that few readers will peruse this monograph without being stirred by the originality and diversity of Professor Schueler's presentation, which testifies to his imaginative power and to his sovereign command over wide fields of knowledge. The uniqueness of this book relates to the fact that it constitutes, as far as I am aware, the only attempt of a single author to explicitly state, and illustrate with examples, the working principles of a scientific field which cuts across boundaries of traditional specialties. Professor Schueler exposes the principle of blending different levels of analysis and different levels of linguistic representation to the interdisciplinary approach of chemobiodynamics, a term used to designate the concept of control of biologic events by drugs. Through emphasis on differences in levels of organization, with corresponding differences in emergent properties at each level, many of the ambiguities pertaining to structure-activity considerations are put into their proper perspective, and important sources of confusion as well as pitfalls of logic are lucidly exposed. In this attempt, he appeals much more to imagination, intuition, and the psychology of scientific thinking than to abstract and rigorous exposition of epistemic principles.

Obviously to ensure complete comprehension of this process of crossing disciplinary boundaries, a considerable amount of space is dedicated to discussions on the structure of matter, on physical and chemical theories of bonding, on questions of biologic measurement and statistics, and on chemical kinetics. With reference to some of these sections, the question can be raised whether it would not have been in the interest of the otherwise easily flowing principal theme to either condense them or to attach them in the form of separate appendices. However, Professor Schueler may have been motivated to adopt the organization of the presentation by the desire to see the text used by graduate students of pharmacology. This desire, I strongly believe, will be shared by everybody engaged in the teaching of pharmacology.

It is rewarding to examine Professor Schueler's position with respect to trends in contemporary thinking. Some ideas of gen-

eral system theory, mostly based on Ashby's exposition, are very successfully assimilated; probably Professor Schueler's sensitivity to linguistic confusion arising from the interdisciplinary nature of chemobiodynamics prompted a search for a unifying linguistic tool of great generality, a tool which he clearly shows can be provided by the general system theory. In what seems a heretical proposal on the entropy arrow pointing toward order rather than chaos, Professor Schueler is seconded by Stafford Beer. Professor Schueler's keen sense for sharp analysis does not overlook the general proposition of biologic measurement, i.e., to obtain quantitative data in situations in which the number of reacting entities is much smaller than statistical thermodynamics of physical systems demands. Accordingly, the problem of representative measurement in biologic systems, unlike that in physical systems, generally faces the dilemma that the number of possible states of a system is much smaller than the number of its behavior-controlling, independent variables. This view closely resembles Elasser's "principle of finite classes." Both authors, therefore, seem to agree that while averages are physically meaningful so far as macroscopic properties of inorganic systems are concerned, there would be required a novel concept of individual-class membership relations in the biologic domain. Unless I interpret Professor Schueler's intention incorrectly, I find it difficult to reconcile these implications with his apparent adherence to Spencer's doctrine of unification of inorganic and organic nature. In this as well as in other instances, it seems to me that Professor Schueler does not carry his attractive ideas to a satisfactory end point and that he leaves much of what seems to have been on his mind unwritten. For instance, it would seem to me that the sketch of an approach to drug design and characterization of drug action based on information theory would have been worthy of much more extensive elaboration because of its novelty and apparent usefulness as a classificatory and heuristic principle in chemobiodynamics. On the other hand, however, I fail to see the virtue and, indeed, the correctness of viewing the deductive-inductive principle of predictive thinking as a stochastic process. Or to take an example from chemical kinetics, when discussing the kinetics of linear and cyclic reaction chains, the peculiarity of the latter as compared with the former is pointed out; but I would have thought it more pertinent in this connection to extend the discussion to open systems and flow equilibrium rather than to suddenly switch the topic and leave the reader in doubt about what, actually, "topologic biochemistry" signifies. The problems concerning cell membrane permeability are very conveniently listed and classified; but, while an elaborate picture is developed on possible structural configuration of membranes, only passing reference is made to Donnan and transmembrane potentials.

Apparently, Professor Schueler planned the first part of this book, i.e., the first 400 pages, as an introduction into the manifold considerations which provide, in most general terms, the matrix for the pursuit of chemobiodynamics. In fact, it conveys the attitude of mind and the background information which, one expects, would be put to work in the second part, "Drug Design." This expectation is fulfilled in some areas more than in others.

As one would expect, Professor Schueler provides a comprehensive and profound exposition of the "principle of variation" in drug design and very lucidly expresses his ideas on statistical distributions of molecular configurations in relation to drug-receptor interactions. Two comments on this section seem in order. One relates to the construction of isobols for drug combination, which he attributes to Gaddum although S. Loewe as early as 1927 published extensively on the usefulness of isobolograms for the description of drug interactions. The second comment relates to the derivation of the intramolecular length distribution function. Professor

Schueler bases his derivation essentially on the Guth-Mark model of long chain, uncharged polymers, while the work of E. Gill would indicate that this model is of limited validity for relatively short chain, bisquaternary compounds unless some correction factors are introduced. The quantitative treatment of the drug-receptor combination follows strictly the lines set out by Clark and does not refer to the modifications proposed by Ariens and Stephenson. One wonders whether the general orientation of this book would not have made necessary a more complete exposition of the Ferguson principle than it, in fact, received.

The remainder of the second part essentially consists of fairly general considerations of drug actions in complex biologic systems and of the rational of drug mixtures. A collection of well-chosen problems and exercises and some thoughtful statements on training for chemobiodynamics conclude the book.

No simple characterization can do full justice to the book; it contains many illuminating highlights and sketches many deep thoughts. It is probably for this reason that some shortcomings in organization and balance of presentation stand out more clearly than they otherwise would.

Gerhard Werner

An MMPI Handbook, by W. Grant Dahlstrom and George Schlager Welsh. Minneapolis, 1960, University of Minnesota Press. 559 pages. $8.75.

This work is dedicated to S. R. Hathaway and J. C. McKinley, who developed the MMPI. It follows an earlier work edited by Welsh and Dahlstrom, *Basic Readings on the MMPI in Psychology and Medicine* (Minneapolis, 1956, University of Minnesota Press). The new text does not cover the same ground as that work or the well-known *Atlas for the Clinical Use of the MMPI* (Hathaway, S. R., and P. E. Meehl, Minneapolis, 1951, University of Minnesota Press). *Basic Readings* is an extensive collation of the derivations of the technique. The *Atlas*, as the name implies, is a storehouse of clinical material. The present work is a complete handbook which has been needed in this field. It opens with a foreword by Hathaway which constitutes a succinct but cogent critique of the technique, including its more disappointing aspects as well as its merits, and then proceeds logically to administration, interpretation, and applications, closing with an appendix. In the section on administration, the authors adhere closely to *The Minnesota Multiphasic Personality Inventory Manual* (revised edition, New York, 1947, The Psychological Corporation), indeed, quoting extensively from that work. But they include more complete history and discussion than the *Manual.* They also include directions for profile coding as used in the *Atlas*, together with suggested modifications.

The section on interpretations includes a broad range of examples and constitutes a comprehensive review of work in this area, including variations of technique and scoring and the results of these variations. Inescapably, this tends to be highly empirical, and there is little evidence of any attempts at validation of the interpretative assumptions. In this connection, the names of the scales appropriately are played down in that they are designated mainly as numbers and thought of as constructs, as Hathaway discusses in the foreword. For those not familiar with the MMPI lore, it should be said that this is in accord with usual MMPI practice. Indeed, a more investigative approach would no doubt be outside the scope of this book. The section on applications is an exhaustive review of the subject. The various approaches are frequently presented with little or no editorial comment. The impression is a strong one of unbiased, noncommittal reporting. The appendix gives a large amount of supplementary information about the technique.

As with any work in the area of human

feeling and emotional illness, one can look at this from two viewpoints. From the empirical viewpoint of clinical psychology and psychiatry, this technique is one avenue of assessment. From a more scientific viewpoint, it leaves a great deal to be desired in terms of demonstrable validity. This *Handbook*, taken on its own terms, fills a longstanding need for an extensive textbook of the MMPI. Taken on a broader scale, it is exactly as valuable and as weak as the technique which it mirrors so well.

Henry B. Murphree

Drugs and Behavior, edited by L. Uhr and J. G. Miller. New York, 1960, John Wiley & Sons, Inc. 676 pages. $10.75.

Among the numerous published symposia on topics in psychopharmacology, this volume occupies a most unusual position in that it has not (or almost not) been invaded by the professional and reverberant symposia speakers or writers to which a recent editorial in this journal ("Anyone for a Symposium") referred. The motivation for bringing together the articles in this volume arose from the editors' recognition of the lack of general conceptual systems for correlating the different operational approaches in psychopharmacology. Very wisely, attempts in this direction are given priority over a concern for premature classification of drugs and their actions.

The book is divided into two sections. Part I contains what the editors considered "the irreducible minimum in the way of background orientation for the reader who could not reasonably be expected to be conversant with more than one of the many fields that converge at Psychopharmacology." A profound and circumspect discussion of drugs as tools in behavioral research (Russell) and an introduction into physiologic and biochemical actions of psychoactive drugs is followed by several articles dealing with what one could call the theory of measurement in clinical psychopharmacology; apart from more technical papers on various aspects of the design of drug evaluation and on the devices of controls and statistics to ensure the validity of their results, this section also contains a contribution to the psychoanalytic approach in psychopharmacology (Kubie). Furthermore, Pollard and Bakker do justice to the existentialist viewpoint in the pharmacologic treatment of psychiatric disorders, and Cole arouses awareness for the complex topic of behavioral toxicity.

Part II consists essentially of three kinds of articles: short descriptions of methods in animal behavioral studies and of the effects of psychopharmacologic agents in these tests; reports on measurements of, and drug effects on, various psychomotor functions in man; and expositions on integrating conceptual systems in psychopharmacology. Dimensional analysis of human behavior (Eysenck and Cattell), Pavlovian reflexology in man (LeGuillant), and the possible sociologic impact of psychoactive drugs (Nowlis and other authors) are discussed. The usefulness of controlled subjective measures of drug effects on the one hand and their definition by objective measurement in "man-machine systems" on the other are clearly exposed by several groups of authors.

This well-integrated collection of articles conveys a balanced picture of the complexities of psychopharmacology and gives an unprejudiced testimony of the fascinating intellectual challenge and important practical issues that are posed by them.

Gerhard Werner

Concepts of Medicine, edited by B. Lush. New York, 1961, Pergamon Press, Inc. 286 pages. $8.50.

I used to wonder what happened to addresses given at the openings and commencement exercises of colleges and the like; now I know. They get published in collections. This is one. When the addresses

are summaries of the orators' work, they are often useful although usually they lack the fire of the initial writings. Too often, however, the distinguished orator is pressured into addressing his audience on a subject on which he is no great expert or to which his work at best has only some tangential connection. This applies to many of the essays in this collection. As a consequence, many are dull and some are uninformative. Very few indeed are inspiring.

What I cannot really understand is why these essays were gathered together—there is nothing special about the collection as a whole; it does not build up to anything; its organization does not lead anywhere in particular. It is not clear at all to me what concepts in medicine the editor had in mind when he brought together this group of essays ranging from the very recent ones to one nearly 20 years old by American and British medical scientists. One on "Medicine Tomorrow," published in 1942, should at this advanced date surely have been entitled at least "Medicine Today."

Of the twenty-one essays, I found only one, "A Critique of Criticism in Medicine and the Biological Sciences," by William B. Bean in 1958, truly original, stimulating, interesting, and unusual.

Walter Modell

Books received

Altman, P. L., Compiler, and Dittmer, D. S., Editor: Blood and Other Body Fluids, Washington, D. C., 1961, Federation of American Societies for Experimental Biology. 540 pages. $10.00.

Bourne, G. H., Editor: The Structure and Function of Muscle, vol. 3, Pharmacology and Disease, New York, 1960, Academic Press, Inc. 489 pages. $14.00.

Clark, R. L.: Cancer Chemotherapy, Springfield, Ill., 1961, Charles C Thomas, Publisher. 253 pages. $10.50.

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Harris, R. J. C., Editor: Biological Approaches to Cancer Chemotherapy, London, 1961, Academic Press, Inc. 431 pages. $14.00.

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Correspondence

In the May-June, 1961, issue, Dr. Shideman is disturbed by "conflicting reports" on the hypnotic efficacy of methylparafynol, citing my study's failure to detect significant hypnosis after doses as high as 1 Gm. (J. Pharmacol. & Exper. Therap. 111:9, 1954) and then contrasting Thomson's experiment (Brit. M. J. 2:1140, 1958) in which 400 mg. of methylparafynol was allegedly as good as 100 mg. of secobarbital. It so happens that the discrepancy rather readily disappears if one pays attention to the drugs employed in the two studies. Thomson used not methylparafynol (Dormison) but *methyprylone* (Noludar), a drug whose potency is generally accepted to be of the order of magnitude reported by Thomson (see Lasagna, L.: The newer hypnotics, M. Clin. N. America, March, 1957). In fact, the very first paragraph of Thomson's paper refers to two earlier papers on this drug, one of them being my own (J. Chron. Dis. 3:122, 1956).

It has been gratifying to those of us interested in controlled clinical trials to see how good the agreement is between investigators studying the same drugs in different patients, under different circumstances, utilizing different criteria for response, etc. A review of the world literature on properly controlled hypnotic studies in man is quite reassuring about procedures used to assess hypnotic agents clinically. In contrast, the *uncontrolled* clinical hypnotic trial is usually almost totally uninterpretable. The 1954 study on methylparafynol referred to above was the first *controlled* clinical hypnotic trial and also the first report to question the efficacy of this agent. Despite many previous glowing testimonials, the agent is now generally considered ineffective ". . . in any but the mildest insomnias." (The latter quote is from the writings of an early enthusiast who might have been saved the need for recanting if his first trial had been a controlled one.)

The techniques for evaluating hypnotic drugs in man are far from perfect. They are nevertheless reasonably satisfactory when employed properly.

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Antacids

The need for antacid therapy has been experienced at some time by nearly every member of the human race. It probably all began when the first man devoured his food in haste while trembling in a cave at the roars of the saber-toothed tiger outside. Certainly, there has existed a persistent and steadily growing need for preparations that soothe indigestion and relieve pyrosis and pain emanating from the stomach. The first antacid was unquestionably milk, and it continues to be as popular today as it was in the beginning. It has been used in various forms and combinations with such success that new preparations containing it continue to appear, the latest one only recently being released for prescription use.

The early qualitative work of the remarkable William Beaumont on the gastric juice of Alexis St. Martin, in the early nineteenth century, convinced him that the acid secreted by the human stomach was hydrochloric. This finding was later confirmed by the careful quantitative analysis of gastric juice by Bedder and Schmidt in 1885, and thus the stage was set for antacid therapy.

Sodium bicarbonate

Nicolas LeBlanc in 1787 had already prepared the way for the most widely used antacid when he devised a method for preparing sodium carbonate, the precursor of sodium bicarbonate, from sodium chloride. He was established in business as a manufacturer of sodium carbonate by the Duke of Orleans in 1791. Two years later, the Duke was guillotined, and although LeBlanc escaped the same fate, his business was confiscated by the friends of liberty, equality, and fraternity. He finally died by suicide in 1806. However, after England repealed the salt tax, a LeBlanc process factory was established there around 1823, and consequently by 1825, and most certainly by 1855 when the first of the many Solvay processes was developed, there was an abundance of sodium bicarbonate available to neutralize the acid of millions of human stomachs.

Sodium bicarbonate early proved to be a highly effective antacid and is still the most widely used by the laity. Although on occasions there is still some merit in its use medically, for the most part, it has been abandoned by the medical profession. About the only situation in which it is used today with satisfaction by the skilled physician is in the patient with good renal function who has a painful gastric or duodenal ulcer which is slow in healing because the usually employed aluminum compounds are incapable of maintaining sufficiently neutralized gastric juice. In this situation, sodium bicarbonate in combination with calcium carbonate or magnesium oxide (the old Sippy powders) frequently effects almost immediate relief and speeds up the healing, but even so, its use is usually for a limited period of a few days or a week. Once the pain has been relieved and sufficient healing has occurred, the treatment can then be continued with the less effective neutralizers of the aluminum series.

The popular Sippy powders introduced in 1915 were soon modified by many clinicians, but sodium bicarbonate remained the basic ingredient. Their popularity began to fade in the late 1920s and early 1930s when more and more cases of systemic alkalosis were being observed. It soon became recognized that patients with any degree of renal damage were subject to systemic alkalosis, and not a few fatalities occurred during this time.

Aluminum compounds

In 1929, aluminum hydroxide was introduced as an antacid, and soon there appeared a whole series of modifications. One gram of dried aluminum hydroxide gel will neutralize 250 ml. of 0.1N hydrochloric acid. Aluminum compounds, usually given as liquid, viscous, colloidal suspensions, act mainly as buffers by neutralizing hydrochloric acid according to the formula

$$Al(OH)_3 + 3HCl \rightleftarrows AlCl_3 + 3H_2O.$$

Aluminum hydroxide as well as the aluminum chloride produced affords some astringent, demulcent, and protective action, and of course, since there is no absorption, no systemic alkalosis has resulted from their use. The buffering action exhibited by aluminum hydroxide permits a reduction of the gastric acidity to approximately pH 4. This degree of neutralization does not completely suppress gastric digestion but is for most situations highly satisfactory. After the aluminum chloride enters the intestine, the chloride is reabsorbed, and insoluble aluminum hydroxide and aluminum phosphate are formed. One undesirable effect of aluminum hydroxide is constipation, which at times is most severe. Occasionally, it leads to the formation of lower bowel impactions or large concretions with lower bowel obstruction. Large doses remove considerable amounts of phosphorus from the patient, but no untoward effects have been observed because of this when the usual doses employed as antacid therapy are given. In situations in which there is an elevated level of phosphates, as in uremia from renal failure, this principle can be used to advantage in lowering blood phosphate levels.

There are listed at least forty preparations of aluminum hydroxide, aluminum phosphate, or dihydroxy aluminum aminoacetate in the 1961 *Physicians' Desk Reference*. This plethora of proprietary items, of which many are mixtures with other antacids, antispasmodics, sedatives, or other drugs, not only has served to confuse the physician but in many instances has led to poor therapy. The inherent difficulties in effectively regulating the dose that immediately appear when two or more agents are combined in a mixture make many such combinations undesirable. There is almost no merit in ever combining an antipasmodic or sedative drug with an antacid preparation. Such combinations usually lead to improper dosage of one or the other ingredient, and thus only a limited number of patients will receive the proper dose of both drugs. Even in these few cases, the changing character of the diseases usually soon makes treatment with the mixture less effective than it would be if each agent were adjusted to its most effective dose at the particular stage in the patient's illness. Aluminum hydroxide used alone, as a gel or in tablets, is not very popular because of the constipation so frequently observed when adequate doses are employed. There is, however, merit in using aluminum hydroxide (Amphojel) alone if the patient who requires an antacid is experiencing diarrhea or has an overactive bowel leading to loose and frequent stools. The constipating effect may prove very useful in initiating therapy in such patients, and as the patient's status changes, he can be shifted to a less constipating preparation. Conversely, in the constipated patient, it is wise to avoid this action. Frequently, magnesium hydroxide, alone or mixtures of aluminum hydroxide with magnesium trisilicate (Gelusil, AMT suspension) or aluminum hydroxide with magnesium hydroxide (Aludrox, Creamalin, Maalox), satisfactorily regulates the constipated bowel. Generally, aluminum hydroxide preparations containing magnesium hydroxide are more satisfactory in overcoming constipation.

The majority of patients receiving an antacid containing aluminum hydroxide will not need a constipating or cathartic preparation but rather one that maintains the usual bowel status. Usually, any of the above preparations prove satisfactory in these individuals. It then becomes a matter of selecting the preparation that is the most palatable and effective for the individual. Because of individual preferences, it is wise to change from one to another until the particular needs of the patient are best met.

Recently, hydrated magnesium aluminate (Riopan) has been made available. It is a true buffer antacid, highly palatable, and as effective as the now commonly used antacids. It is a useful addition to antacid therapy although, at present, it is somewhat more expensive than the older, commonly used preparations.

Although many claims have been made and some physicians prefer preparations such as hydrated magnesium aluminate (Riopan) or those containing dihydroxy aluminum aminoacetate (Alglyn, Alzinox, Robalate), there is no proof that these preparations have any real clinical advantage over the antacids containing aluminum hydroxide.

Calcium compounds

In recent years, interest has again been revived in calcium as an antacid. Although calcium, as calcium carbonate, has been available since ancient times and is exceedingly abundant in Nature as chalk or combined with magnesium carbonate forming dolomite, of which there are entire mountain chains, it has never been a popular antacid. The old Sippy powders used calcium carbonate to good advantage, but as their use declined, so did the use of calcium carbonate.

The inability of the aluminum compounds, either singly or in combination with various magnesium preparations, to effect a satisfactory neutralization of stomach acid in certain situations has brought about this revival of interest in calcium.

Calcium carbonate, as well as other calcium preparations used as antacids, is an effective nonsystemic, nonbuffer antacid. Calcium carbonate acts in the following manner:

$$CaCO_3 + 2HCl \rightleftarrows CaCl_2 + H_2CO_3 \rightarrow CO_2 + H_2O.$$

Calcium preparations when pushed can produce a stomach pH of 7.5. When used clinically, they readily maintain a pH of 4.5 or better. One gram of calcium carbonate will neutralize 210 ml. of 0.1N hydrochloric acid. In the stomach, calcium preparations form calcium chloride, which, as it passes into the intestine, reacts with the sodium bicarbonate there to form sodium chloride and calcium carbonate. The sodium chloride is reabsorbed, and the calcium carbonate, being nearly insoluble, is lost by way of the bowel. Calcium preparations are constipating, form concretions, and like aluminum hydroxide can cause obstipation and on occasion lower bowel obstruction.

At present, only three calcium preparations are in common use. These are calcium carbonate, a recently released mixture of calcium carbonate with milk and the antispasmodic D-calcium pantothenate (Ilomel), and calcium carbonate with glycine (Titralac). The latter has a pleasant taste, effectively neutralizes stomach acid (usually better than pH 4.5), and, if given in effective dosage, may elevate the pH of stomach contents to 7.5. The glycine serves as a rapidly effective buffer to supplement the action of the calcium carbonate. This preparation is gaining favor but is expensive in comparison to the usual aluminum hydroxide

preparation or calcium carbonate. Unquestionably, there is a useful role for calcium in antacid therapy, and there still exists a need for a palatable, inexpensive, calcium-containing antacid agent.

Magnesium compounds

Magnesium, first obtained as the sulfate salt by Nehemiah Grew in 1695 from a mineral spring at Epson, England, has long been used medicinally. In 1755, the illustrious Joseph Black prepared magnesium oxide from magnesium carbonate (magnesia alba), and thus the stage was set for the role of magnesium as an antacid. Magnesium oxide has long enjoyed an important role as an antacid. It exerts far more acid-neutralizing ability than any other antacid. One gram will neutralize approximately 432 ml. of 0.1N hydrochloric acid. No gas is formed, and the pH of the gastric content can be raised to neutrality, at times even higher. Its mode of action is

$$MgO + 2HCl \rightleftarrows MgCl_2 + H_2O.$$

Although most of the magnesium chloride is converted to magnesium carbonate in the intestine and thus excreted, enough remains to exert a cathartic action, and thus magnesium oxide cannot be used alone satisfactorily. Furthermore, there is some danger of magnesium intoxication from absorption when renal impairment is such as to preclude prompt excretion. The role of magnesium oxide as an antacid declined along with that of the Sippy powders, of which it was one of the essential ingredients. It is seldom used today.

Magnesia magma (Milk of Magnesia), a derivative of magnesium oxide, is a preparation containing approximately 8 per cent magnesium hydroxide. It is used widely both by physicians and the laity as an antacid as well as a highly useful, relatively benign cathartic. Ten milliliters of this preparation containing approximately 0.8 Gm. magnesium hydroxide will neutralize approximately 270 ml. of 0.1N hydrochloric acid. It is often given at bedtime to allay acid indigestion and to induce better bowel activity the next day. Its cathartic action is much enhanced by drinking copious amounts of water when it is ingested. As an antacid, magnesium hydroxide has been and still is a very useful agent. At present, it is used widely in suspensions with aluminum hydroxide (Aludrox, Creamalin, Maalox) in which its cathartic effect is balanced in varying degrees, as far as the individual patient is concerned, by the constipating action of aluminum hydroxide. There is sufficient merit in these suspensions to justify their widespread use. If there is any significant effect on the gastrointestinal tract, it is likely to be a mild laxative one. In the occasional patient, diarrhea may be seen after their use.

The chemical combination of magnesium oxide with silicon dioxide, forming magnesium trisilicate, made available yet another useful magnesium preparation for antacid therapy. Although not as effective an acid neutralizer as magnesium oxide (1 Gm. neutralizes approximately 140 to 160 ml. of 0.1N hydrochloric acid in 4 hours at 37° C.), it is a useful nonsystemic antacid and also exerts useful absorbent properties. Its mechanism of action is

$$2MgO + 3SiO_2 + H_2O + 4HCl \rightleftarrows 2MgCl_2 + 3SiO_2 + (x + 2)H_2O.$$

The magnesium chloride is converted mainly to magnesium carbonate in the intestine, but enough magnesium chloride usually remains to lead to loose bowel movements if the dose of magnesium trisilicate is large. Because of this undesirable effect, magnesium trisilicate is combined with aluminum hydroxide for

best effect. Various useful preparations containing these agents in suspension are available (AMT suspension, Gelusil, Trisogel). Generally, these preparations are so balanced between the constipating action of aluminum hydroxide and the cathartic action of magnesium trisilicate as to be devoid of any serious effect either way for the majority of patients. In some patients, constipation may ensue, while in others, looseness or even diarrhea will appear. These individuals must then be shifted to a more constipating or cathartic preparation. Fortunately, there are few patients that fall into either category.

Conclusions

With the above information in mind, it is useful to consider briefly some facts of importance concerning the selection and use of the proper antacid for the individual patient.

1. Evaluate the patient carefully. Is he one who is habitually constipated, or does he have a tendency toward loose stools? The antacid should be chosen with an eye to correcting any abnormal bowel function and to avoid, if possible, creating an unfavorable bowel status.

2. Palatability—the agent should be one that agrees with the patient. Some persons like sweet, mint flavors, others like flat-tasting preparations. Almost every patient approves a smooth, easily swallowed antacid. A too highly flavored or an unpalatable, bitter, or metallic-tasting agent may actually lead to increased gastric acid secretion.

3. Use adequate amounts of the agent, at sufficiently frequent intervals to ensure maximum antacid effect. Frequently, doses of 10 to 20 ml. every 1 to 2 hours are necessary to secure proper control if there is a high level of stomach acid, a gastric ulcer, or a highly painful ulcer anywhere in the stomach or duodenum.

4. Do not hesitate to use a Sippy powder for brief periods or a calcium preparation for longer periods if healing and pain are not controlled by the aluminum preparations. Never use Sippy powders in the presence of renal impairment or for any prolonged period of time.

5. Avoid the use of combinations of antacids with antispasmodics, sedatives, and tranquilizers in the treatment of gastric or duodenal ulceration and for other gastrointestinal conditions. Almost invariably, one or the other ingredient is not being adjusted to the patient's present needs, and consequently maximum therapeutic benefit is not being secured.

6. Always be on the alert to prevent or promptly relieve constipation, diarrhea, or the rare concretion or obstruction that may ensue at any time during therapy with these agents.

7. Since treatment with antacids is usually prolonged, the physician should seek out the most effective and least expensive agent for his patient.

8. Antacids containing magnesium, although usually presenting no problem to the normal kidney, may throw a burden on the diseased kidney. In the presence of severe renal impairment, it is conceivable that magnesium intoxication could occur.

9. Occasionally, patients with chronic ulcer disease on large amounts of milk and antacid therapy complain of severe lower bowel cramps. These cramps are frequently a result of the therapy, and a marked reduction in milk intake and a shift to a calcium preparation or a less cathartic antacid will clear up the situation.

10. Be careful of the effect of antacids on other drugs being given at the same time. For example, calcium and magnesium markedly reduce the absorption of the tetracyclines. Magnesium sulfate, for example, administered with a tetracycline leads to blood levels approximately 25 per cent of those observed without the salt. If a satisfactory response is not being secured by a patient on an active agent, antacid therapy may be the cause.

DALE G. FRIEND, M.D.

Peter Bent Brigham Hospital
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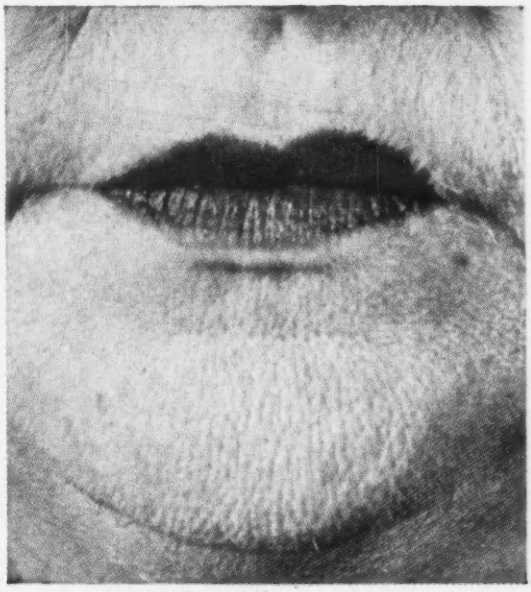

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References: 1. Edelstein, A J.: Pennsylvania M. J. *62*:1831 (Dec.) 1959. 2. Smith, J. G., Jr.; Engel, M. F.; and Blank, H.: J. Florida M. A. *46*:960 (Feb.) 1960. 3. Robins, H. M.: New York J. Med. *61*:717 (Mar. 1) 1961.

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